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A diastereodivergent strategy for the asymmetric syntheses of (−)-martinellic acid and (−)-4-*epi*-martinellic acid

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ABSTRACT

Asymmetric syntheses of (−)-martinellic acid and (−)-4-*epi*-martinellic acid were achieved in 20 steps from commercially available starting materials using a diastereodivergent strategy. The conjugate addition of lithium (*R*)-*N*-allyl-*N*-(α-methyl-*p*-methoxybenzyl)amide to *tert*-butyl (*E*)-3-[2′-(*N*,*N*-diallylamino)-5′-bromophenyl]propenoate and alkylation of the resultant β-amino ester with methyl bromoacetate were used as the key steps to install the C(9b) and C(3a) stereogenic centres, respectively. Subsequent cyclisation to the corresponding pyrroloquinolin-2-one and reduction of the C(4)-carbonyl group was followed by two complementary procedures for olefination and concomitant intramolecular Michael addition, which gave both C(4)-epimers of this tricyclic molecular architecture in >99:1 dr. Subsequent elaboration of these templates provided access to (−)-martinellic acid and, for the first time, (−)-4-*epi*-martinellic acid.

1. Introduction

In 1995 Witherup et al. isolated the highly functionalised pyrroloquinoline alkaloids (−)-martinellic acid **1** and (+)-martinelline **2** from the species *Martinella iquitoensis*,[1] a plant cultivated by South American tribes for use as a treatment for eye ailments.[2] The ground root extracts of these species are said to eventually cure conjunctivitis,[3] an effect that was first documented in 1791.[2,4] The individual biological activities of **1** and **2** have been assessed, and it was noted that (+)-martinelline **2** showed a much higher inhibitory aptitude for bradykinin receptors compared to (−)-martinellic acid **1**, as well as increased antimicrobial properties.[1] The interesting medicinal properties of **1** and **2** combined with their unique fused pyrroloquinoline structure have spurred research into the synthesis of this tricyclic molecular architecture,[5] as well as numerous analogues,[6] with several total[7,8] and formal[9,10] syntheses of **1** and **2** having been reported to date (Fig. 1).[11]

As part of our ongoing research programme concerning the conjugate addition of enantiopure secondary lithium amides (derived from α-methylbenzylamines) to α,β-unsaturated esters,[12] and in particular the application of this methodology in the total syntheses of natural products,[13] we became interested in the tricyclic molecular architecture within (−)-martinellic acid **1**. Upon retrosynthetic analysis of (−)-martinellic acid **1**, 'Ma's intermediate' **3**·*x*HCl[7a,8a] was identified as our initial target and we proposed that a double aza-Michael strategy could be used to access the tricyclic core within **3**·*x*HCl. There are various reports in the literature concerning the introduction of a C(4) sidechain into a pyrroloquinoline or pyrroloquinolin-4-one scaffold (such as **6**), although in no instance has the product been fully elaborated to either (−)-martinellic acid **1** or (+)-martinelline **2**.[5k,10a,c,14] In our alternative diastereodivergent approach both (−)-martinellic acid **1** and its C(4)-epimer would both be accessible from **6**: it was expected that reduction of **6** would give the corresponding hemiaminal, which upon reaction with a suitable olefination reagent would generate α,β-unsaturated ester **5**, which would then undergo in situ intramolecular aza-Michael addition to generate the C(4) stereogenic centre within **4**. Furthermore, the resultant ester substituent within **4** would provide a functional handle for the construction of the 3-aminopropyl moiety found within **3**·*x*HCl. It was envisaged that

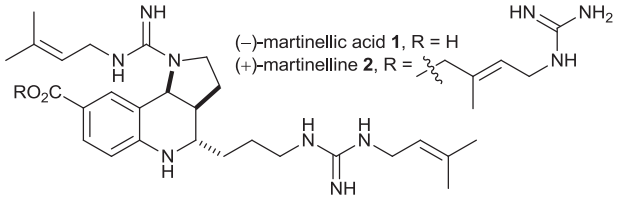

Fig. 1. The structures of (−)-martinellic acid **1** and (+)-martinelline **2**.

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pyrroloquinoline **6** could be accessed via cyclisation of β-amino ester **7**, which, in turn, could be produced from α,β-unsaturated ester **8** and enantiopure lithium amide **9** using our diastereoselective aza-Michael reaction, followed by alkylation of the resultant β-amino ester, and therefore install the correct stereochemistry at the C(3a) and C(9b) stereogenic centres within the target molecules (Fig. 2). We describe herein our full investigations within this area, which culminate in the development of asymmetric syntheses of (−)-martinellic acid **1** and its C(4)-epimer, part of which has been communicated previously.[15]

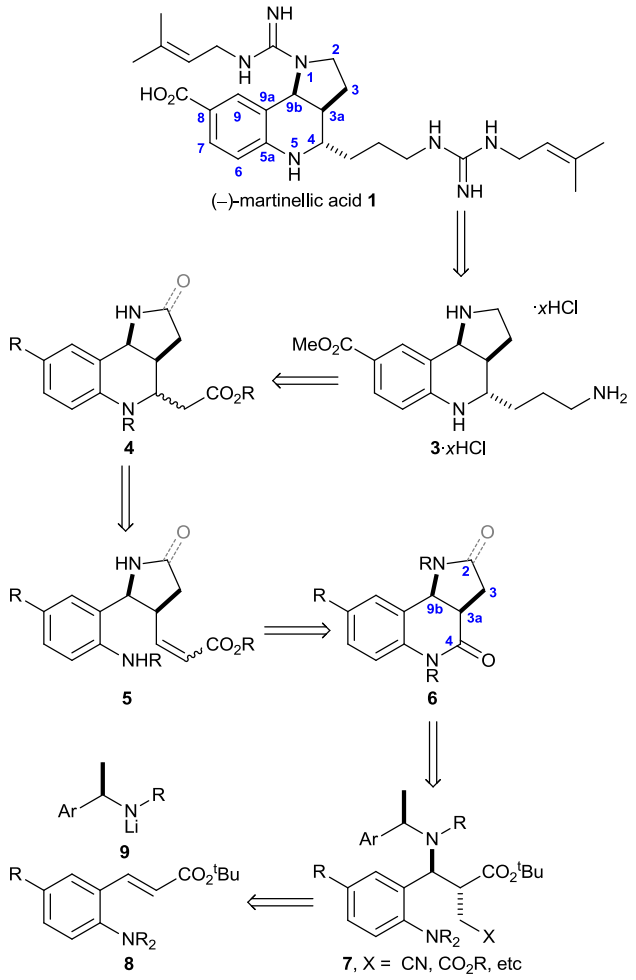
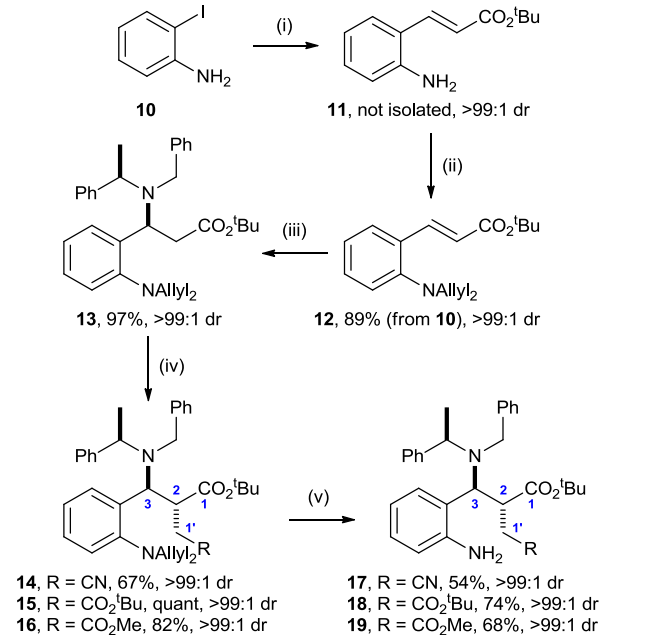


Fig. 2. Retrosynthetic analysis of (−)-martinellic acid **1**.

2. Results and discussion

2.1. Model studies: introduction of the C(3a) and C(9b) stereocentres

In the first instance, an asymmetric synthesis of a model pyrroloquinoline scaffold which lacked the C(8)-carboxyl group was investigated. Initial efforts were therefore directed at the optimisation of the synthesis of α,β-unsaturated ester **12**. Heck coupling of commercially available 2-iodoaniline **10** and *tert*-butyl acrylate in the presence of $Pd(OAc)_2$ and P(*o*-Tol)$_3$ in MeCN at 70 °C for 16 h proceeded to full conversion, to give **11**[6g] in >99:1 dr [(*E*)/(*Z*)]. An analytically pure sample of **11** was obtained in 85% yield after purification of the crude reaction mixture; however, it was found that purification of aniline **11** after the Heck coupling was unnecessary as a superior yield of **12** could be obtained if **11** was used directly in the next step, without purification.[16] In this case, bis-N-allylation of **11** was achieved by treatment with excess allyl iodide and K_3PO_4 in acetone at reflux for 48 h, which gave **12** in 89% isolated yield (from **10**) and >99:1 dr; this method was amenable to the synthesis of α,β-unsaturated ester **12** in ~25 g scale batches. Conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to α,β-unsaturated ester **12** in THF at −78 °C gave β-amino ester **13** in 97% yield and >99:1 dr. The relative configuration within **13** was assigned by analogy to the established stereochemical outcome of this class of conjugate addition reactions,[12] and by reference to our transition state mnemonic, which was developed to rationalise the diastereoselectivity observed upon conjugate addition of enantiopure lithium amides derived from α-methylbenzylamine.[17] Treatment of β-amino ester **13** with LDA, followed by addition of bromoacetonitrile gave **14** in 80:20 dr, and 67% yield and >99:1 dr after purification via flash column chromatography. Analogous alkylation of **13** with either *tert*-butyl bromoacetate or methyl bromoacetate gave **15** and **16** as single diastereoisomers (>99:1 dr), which were isolated in quantitative and 82% yield, respectively.[18] With a range of suitably functionalised substrates **14**–**16** in hand, attention was turned to their deprotection and cyclisation to give the corresponding dihydroquinolin-2-ones. N-Deallylation of **14**–**16** was achieved by employing a Tsuji–Trost reaction with $Pd(PPh_3)_4$ and *N*,*N*-dimethylbarbituric acid (DMBA) as the allyl cation scavenger; DMBA is particularly effective for this purpose, as excess DMBA can be removed from the crude reaction mixture by extraction into aqueous solutions of K_2CO_3. Treatment of **14** with 5 mol % $Pd(PPh_3)_4$ and DMBA in CH_2Cl_2 at 35 °C for 16 h gave **17**, which was isolated in 54% yield and >99:1 dr. Analogous reaction of **15** and **16** gave **18**, in 74% isolated yield and >99:1 dr, and **19** in 68% isolated yield and >99:1 dr, respectively (Scheme 1). The relative configuration within **19** was established unambiguously by single crystal X-ray diffraction analysis (Fig. 3),[19] and the absolute (2*R*,3*S*,α*R*)-configuration within **19** was assigned relative to the known (*R*)-configuration of the α-methylbenzyl fragment; this



Scheme 1. Reagents and conditions: (i) $Pd(OAc)_2$, P(*o*-Tol)$_3$, *tert*-butyl acrylate, Et_3N, MeCN, 70 °C, 16 h; (ii) allyl iodide, K_3PO_4, acetone, reflux, 48 h; (iii) lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide, THF, −78 °C, 2 h; (iv) LDA, THF, −78 °C, 1 h then RCH_2Br, −78 °C to rt, 16 h; (v) $Pd(PPh_3)_4$, DMBA, CH_2Cl_2, 35 °C, 16 h.

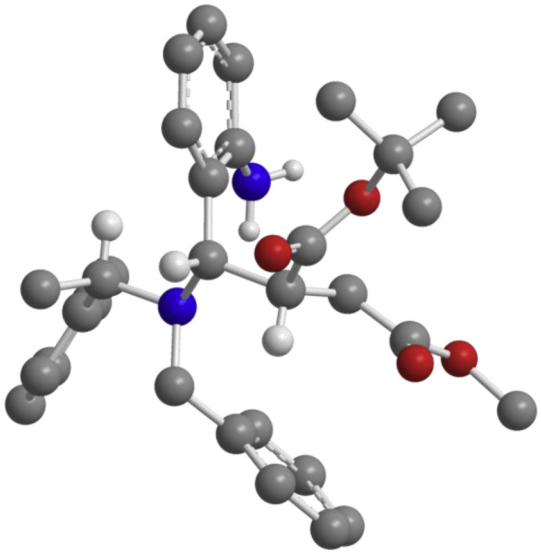


Fig. 3. X-ray crystal structure of **19** (selected H atoms are omitted for clarity).

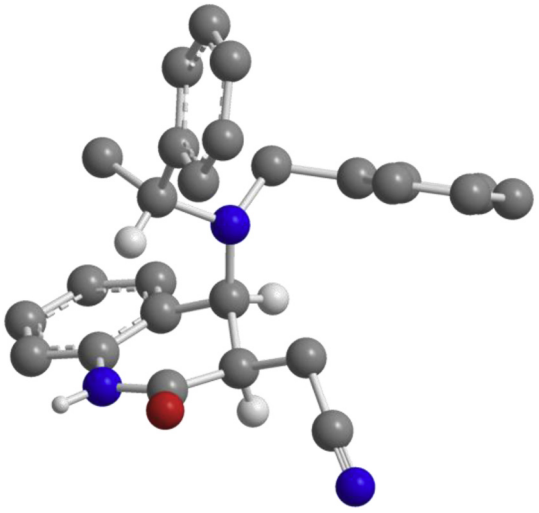
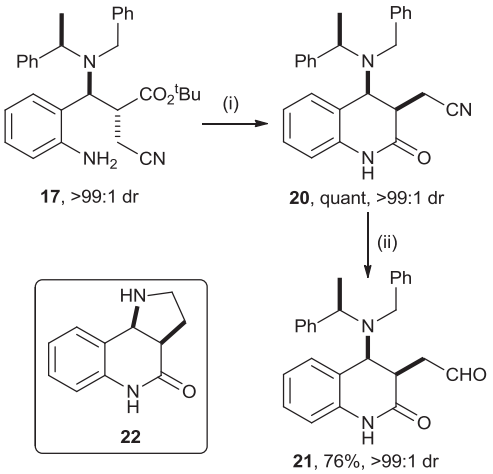


Fig. 4. X-ray crystal structure of **20** (selected H atoms are omitted for clarity).

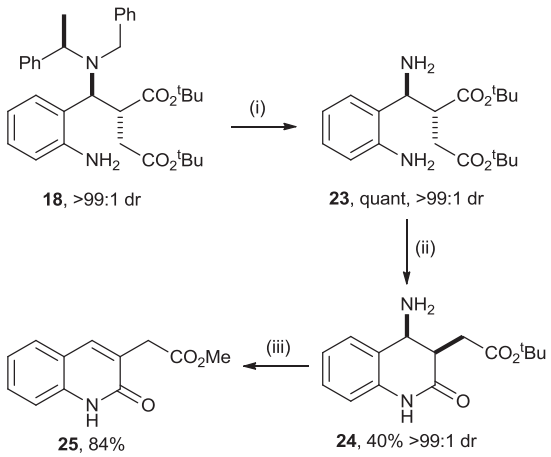
analysis therefore also secured the assigned absolute (2*R*,3*S*,α*R*)- and (3*S*,α*R*)-configurations within **16** and **13**. The configurations within **17** and **18** (and therefore also those within **14** and **15**) were assigned by analogy to those within **16** and **19**; the similarities between the ^{1}H NMR chemical shifts and ^{3}J coupling constants observed for both the C(3)*H* and C(1′)*H* protons within **14**–**19** were consistent with this assumption, and in all cases these assignments were later confirmed unambiguously by single crystal X-ray diffraction analyses of several derivatives.

With **17**–**19** in hand, attention was turned to their cyclisation to give the corresponding dihydroquinolin-2-ones. Several sets of conditions for the cyclisation of **17** were evaluated, and treating **17** with $PhCO_2H$ (3.0 equiv) in THF at 50 °C for 72 h was found to be the optimal procedure, which gave **20** in quantitative yield (Scheme 2). The relative configuration within **20** was unambiguously established by single crystal X-ray diffraction analysis (Fig. 4),[19] and the absolute (3*R*,4*S*,α*R*)-configuration within **20** was assigned relative to the known (*R*)-configuration of the α-methylbenzyl fragment; this analysis also secured the assigned configurations within **14** and **17**. Attention was next turned to the construction of the pyrrolidine ring: reduction of the nitrile group within **20** with DIBAL-H gave aldehyde **21**, which was isolated in 76% yield and >99:1 dr, but attempted hydrogenolysis of **21** (which was anticipated to effect both N-debenzylation and reduction of the in situ formed imine resulting from cyclisation of the primary amino group onto the pendant aldehyde functionality)[20] unfortunately gave only returned starting material. All other attempts to form pyrroloquinolin-4-one **22** from **21** were also unsuccessful (Scheme 2).

Attempted cyclisation of **18** upon treatment with $PhCO_2H$ in THF at 50 °C resulted in returned starting material, and attempted transesterification of **18** to the corresponding bis-methyl ester with $SOCl_2$/MeOH produced a complex mixture of products. However, hydrogenolysis of **18** with $Pd(OH)_2$/C in MeOH under H_2 (4 atm) gave **23** in quantitative yield and >99:1 dr, and attempted chromatographic purification of a portion of **23** resulted in partial cyclisation to dihydroquinolin-2-one **24**, which was isolated in 40% yield and >99:1 dr (Scheme 3). The relative configuration within **24** was established unambiguously by single crystal X-ray diffraction analysis (Fig. 5);[19] these data also secured the assigned configurations within **15**, **18** and **23**. However, all attempts at conversion of **24** to the corresponding pyrroloquinolin-4-one were unsuccessful: substantial decomposition was observed upon treatment of **24** with $PhCO_2H$, treatment of **24** with DBU (5.0 equiv) in CH_2Cl_2 resulted in a complex mixture of unidentified products, and attempted



Scheme 2. Reagents and conditions: (i) $PhCO_2H$, THF, 50 °C, 72 h; (ii) DIBAL-H, CH_2Cl_2, −78 °C, 2 h.



Scheme 3. Reagents and conditions: (i) $Pd(OH)_2$/C, MeOH, H_2 (4 atm), rt, 16 h; (ii) attempted purification; (iii) HCl (2.0 M in Et_2O), MeOH, reflux, 1 h.

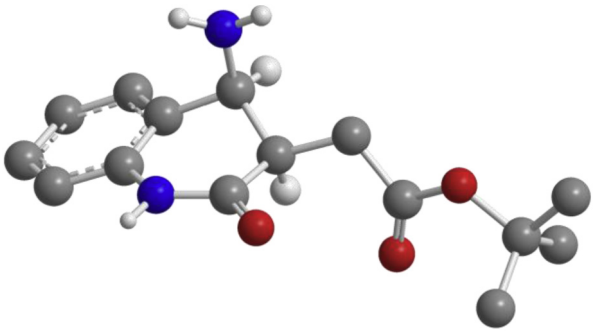
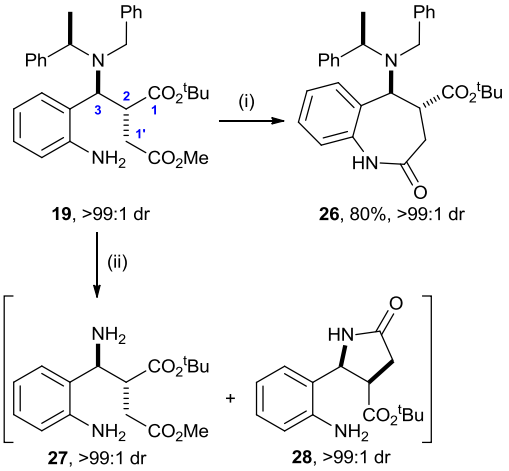


Fig. 5. X-ray crystal structure of **24** (selected H atoms are omitted for clarity).

transesterification of **24** to the corresponding methyl ester gave only **25**[21] which was isolated in 84% yield (Scheme 3).

Attempted cyclisation of **19** to the corresponding dihydroquinolin-2-one, upon treatment with $PhCO_2H$ in PhMe at reflux for 16 h, gave only tetrahydrobenzazepine **26** in 80% yield and >99:1 dr (Scheme 4). The relative configuration within **26** was unambiguously established by single crystal X-ray diffraction analysis (Fig. 6),[19] and the absolute (4*R*,5*S*,α*R*)-configuration within **26** was assigned relative to the known (*R*)-configuration of the α-methylbenzyl fragment. Furthermore, the determination of a Flack *x* parameter[22] of −0.01(15) for the crystal structure of **26** allowed this assignment to be confirmed unambiguously. Meanwhile, hydrogenolytic N-debenzylation of **19** upon treatment with $Pd(OH)_2/C$ gave a 50:50 mixture of **27** and a product which was tentatively assigned as pyrrolidin-2-one **28**, based on ^1H NMR, COSY and HSQC, and mass spectrometric analyses of the crude reaction mixture (Scheme 4). Products arising from incomplete hydrogenolysis of the *N*-benzyl-*N*-(α-methylbenzyl) moiety were also observed under these reaction conditions so the crude reaction mixture was resubjected to the hydrogenolysis reaction conditions, which gave a 39:61 mixture of **27** and **28**, respectively. Heating a solution of this mixture in PhMe at reflux, in an effort to drive the cyclisation reaction to completion, resulted in substantial decomposition to an intractable mixture of products.



Scheme 4. Reagents and conditions: (i) $PhCO_2H$, PhMe, reflux, 16 h; (ii) $Pd(OH)_2/C$, H_2 (1 atm), MeOH, rt, 16 h.

The formation of pyrrolidin-2-one **28** [i.e., cyclisation of a substrate bearing a methyl ester on the C(2) substituent] during N-deprotection of **19** suggested that this approach could be combined with an acid promoted cyclisation to give the corresponding

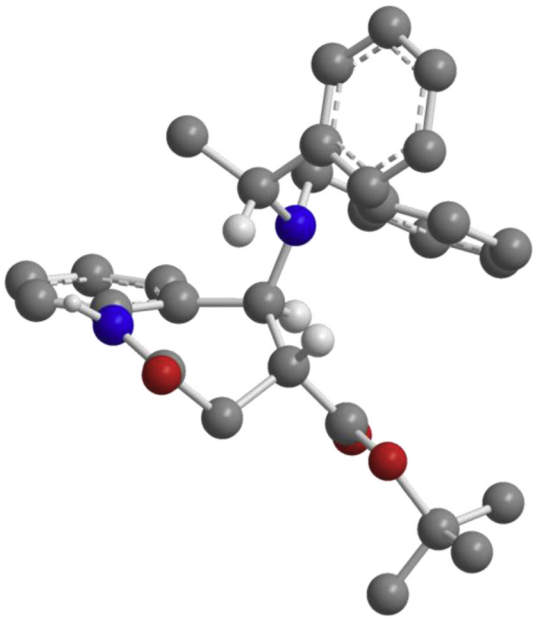
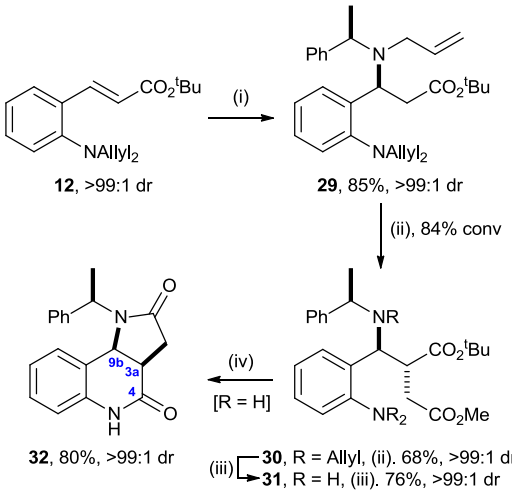


Fig. 6. X-ray crystal structure of **26** (selected H atoms are omitted for clarity).

pyrroloquinolin-4-one and allow both rings to be formed in one step. β-Amino ester **29** was therefore prepared via conjugate addition of lithium (*R*)-*N*-allyl-*N*-(α-methylbenzyl)amide[23] to α,β-unsaturated ester **12**, which gave β-amino ester **29** in 85% yield and >99:1 dr. Deprotonation of **29** with LDA followed by alkylation with methyl bromoacetate proceeded to 84% conversion, giving **30** in 68% yield and >99:1 dr after purification. N,N′-Deallylation of **30** was then achieved by treatment with $Pd(PPh_3)_4$ and DMBA, which gave **31** in 76% isolated yield and >99:1 dr. Subsequent treatment of **31** with $PhCO_2H$ gave pyrroloquinolin-4-one **32** as the sole reaction product, which was isolated in 80% yield and >99:1 dr (Scheme 5).

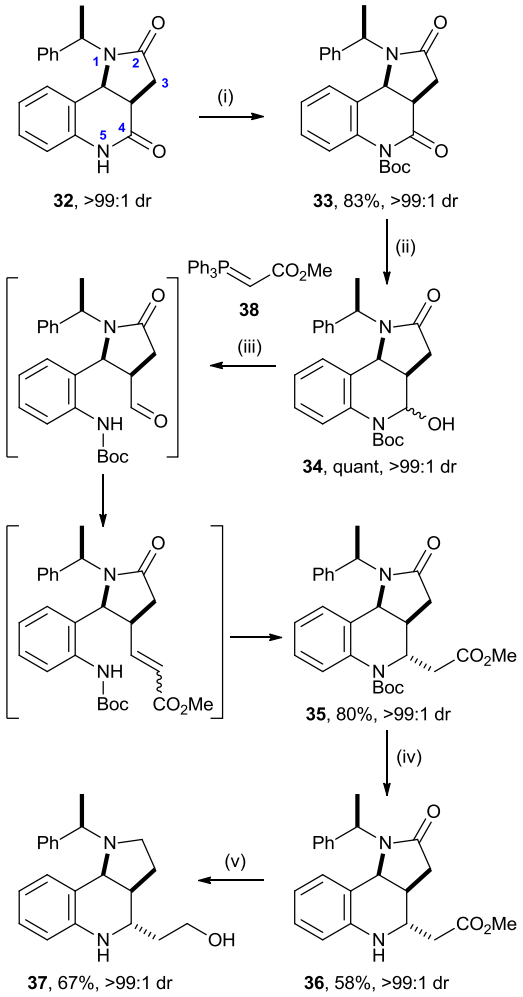


Scheme 5. Reagents and conditions: (i) lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)-amide, THF, −78 °C, 2 h; (ii) LDA, THF, −78 °C, 1 h then methyl bromoacetate, −78 °C to rt, 16 h; (iii) $Pd(PPh_3)_4$, DMBA, CH_2Cl_2, 35 °C, 16 h; (iv) $PhCO_2H$, PhMe, reflux, 16 h.

2.2. Model studies: introduction of the C(4) substituent

With enantiopure pyrroloquinolin-4-one **32** in hand, attention was turned to the introduction of the required stereochemistry at the C(4) position. It was anticipated that in order to achieve chemoselective reduction of **32** at C(4) [rather than at C(2)], the C(4)

carbonyl group would need to be activated by the introduction of an electron withdrawing protecting group on the *N*(5) atom. Thus, treatment of **32** with Boc_2O, DMAP and Et_3N in CH_2Cl_2 gave **33** in 83% isolated yield (Scheme 6). The relative configuration within **33** was determined unambiguously by single crystal X-ray diffraction analysis (Fig. 7),[19,24] and the absolute (3a*R*,9b*S*,α*R*)-configuration within **33** was assigned from the known (*R*)-configuration of the α-methylbenzyl fragment. Reduction of **33** with $LiAl(O^tBu)_3H$ gave complete conversion to hemiaminal **34** as a single diastereoisomer [of undetermined configuration at C(4), >99:1 dr] in quantitative yield, without any detectable reduction of the amide functionality at C(2). Under optimised conditions, treatment of **34** with phosphorane **38** in PhMe at 80 °C for 72 h effected both olefination and in situ intramolecular aza-Michael addition to give **35** in >99:1 dr, and 80% yield and >99:1 dr after purification. Deprotection of the *N*-Boc group within **35** was achieved by treatment with TFA in CH_2Cl_2, which gave **36** in 58% yield and >99:1 dr. Subsequent reduction of **36** upon treatment with $LiAlH_4$ gave **37** in 67% yield and >99:1 dr (Scheme 6). The relative configuration within **36** was determined unambiguously by single crystal X-ray diffraction analysis (Fig. 7),[19] and the absolute (3a*S*,4*S*,9b*S*,α*R*)-configuration within **36** was assigned from the known (*R*)-configuration of the α-methylbenzyl fragment. This analysis therefore also established the assigned configurations within **35** and **37**.



Scheme 6. Reagents and conditions: (i) Boc_2O, DMAP, Et_3N, CH_2Cl_2, 35 °C, 16 h; (ii) $LiAl(O^tBu)_3H$, THF, 0 °C, 1 h; (iii) **38**, PhMe, 80 °C, 72 h; (iv) CH_2Cl_2/TFA (10:1), 35 °C, 4 h; (v) $LiAlH_4$, THF, reflux, 16 h.

2.3. Attempted elaboration to 'Ma's intermediate'

Initial attempts to activate the alcohol functionality within **37** as the corresponding tosylate gave a mixture of products including tosylate **39** and chloride **40**, which were isolated in 41 and 23% isolated yield, respectively. The formation of a chloride, such as **40**, from an alcohol upon attempted tosylation is unusual, although this phenomenon has been noted in related systems.[25] Alternatively, subjecting **37** to an Appel reaction gave chloride **40** as the sole product in 72% yield and >99:1 dr after purification of the crude reaction mixture. Initial attempts at the bromination of **40** at the C(8) position, under the conditions reported by Miyata et al. for the bromination of a related substrate,[10d] resulted in a complex mixture of products being formed, which included mono- and dibrominated products **41** and **42**.[26] However, the slow addition of a solution of NBS to a solution of **40**, followed by stirring the resultant mixture for 1 h at rt gave **41** and **42** in 68 and 6% isolated yield, respectively, after purification (Scheme 7). The aromatic substitution pattern within **42** was assigned by ^1H NMR spectroscopic analysis, with the ^1H NMR ^4J coupling constant (2.2 Hz) between the C(7)*H* and C(9)*H* protons suggesting a *meta* relationship between the protons on the aromatic ring, consistent with the strong *ortho* and *para* directing ability of anilines.

It was anticipated that **3**·*x*HCl could be obtained from **41** by (i) methoxycarbonylation of the aryl bromide moiety; (ii) displacement of the chloride by cyanide; and (iii) global hydrogenolysis under acidic conditions. Thus, treatment of **41** with $Pd(OAc)_2$ and Xanpthos under CO (1 atm) at 70 °C for 16 h proceeded to give ~50% conversion to **43**. Resubjection of the crude reaction mixture to the methoxycarbonylation reaction conditions proceeded with full conversion to give **43**; however, separation of **43** from the residual Xantphos ligand hindered the purification and **43** was isolated in only 17% yield. Subsequent treatment of **43** with NaCN in DMSO at 90 °C gave **44** in 79% yield and >99:1 dr. Typical

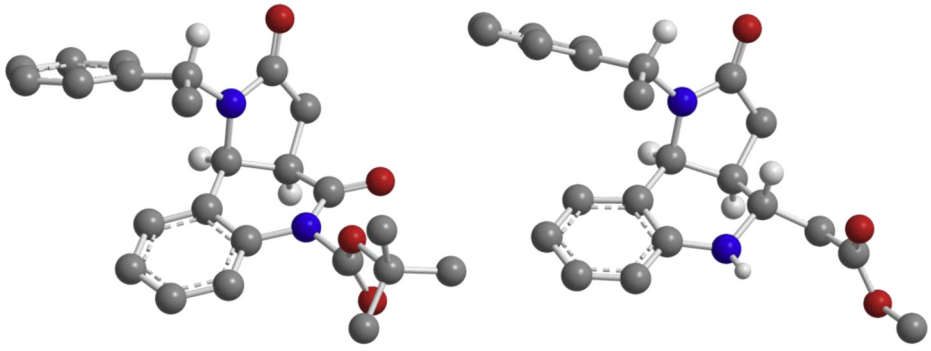
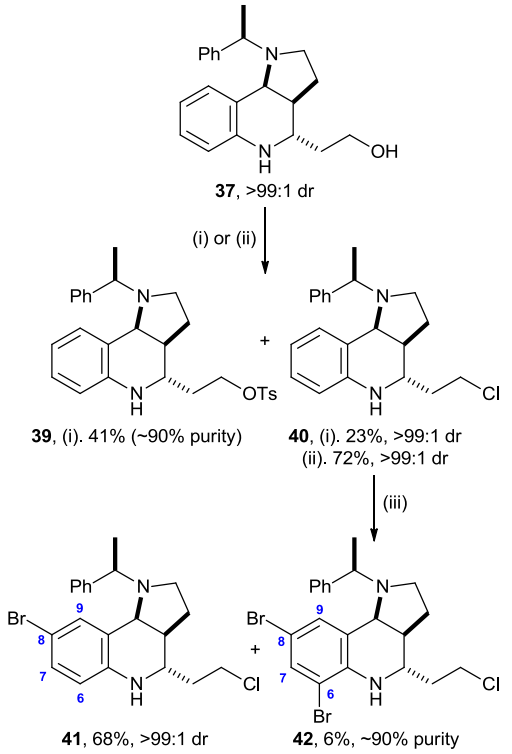
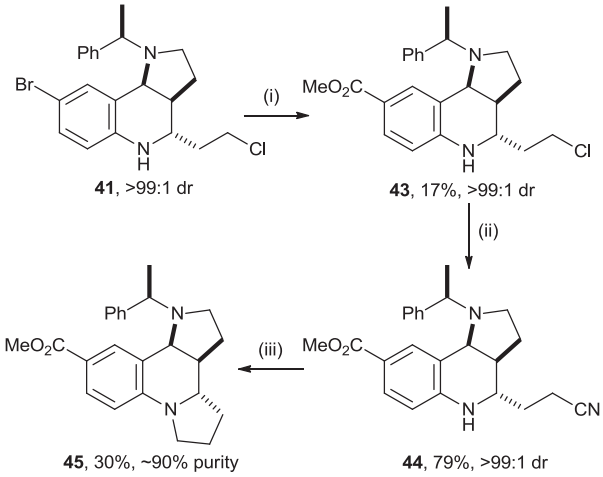


Fig. 7. X-ray crystal structures of **33** [left] and **36** [right] (selected H atoms are omitted for clarity).



Scheme 7. Reagents and conditions: (i) TsCl, DMAP, Et_3N, CH_2Cl_2, rt, 16 h; (ii) CCl_4, PPh_3, Et_3N, MeCN, rt, 16 h; (iii) NBS, MeCN, 0 °C to rt, 2 h.

conditions for the deprotection of *N*-α-methylbenzyl groups are treatment of the substrate with $Pd(OH)_2/C$ in MeOH under H_2 (1 atm) for 16 h,[12] conditions which are also known to effect the reduction of nitriles to the corresponding primary amines.[27] It was also desirable to trap the triamine product **3** as the corresponding hydrochloride salt, as the free amine has been reported to be unstable and difficult to handle.[8a] However, treatment of **44** with $Pd(OH)_2/C$ in methanolic HCl under H_2 (1 atm) gave a mixture of products within which the major product was identified as tetracycle **45**. Purification of the crude reaction mixture gave **45** in 30% yield and ~90% purity (Scheme 8).[28] This route was therefore abandoned in favour of a strategy which incorporated protection of the *N*(5) atom.



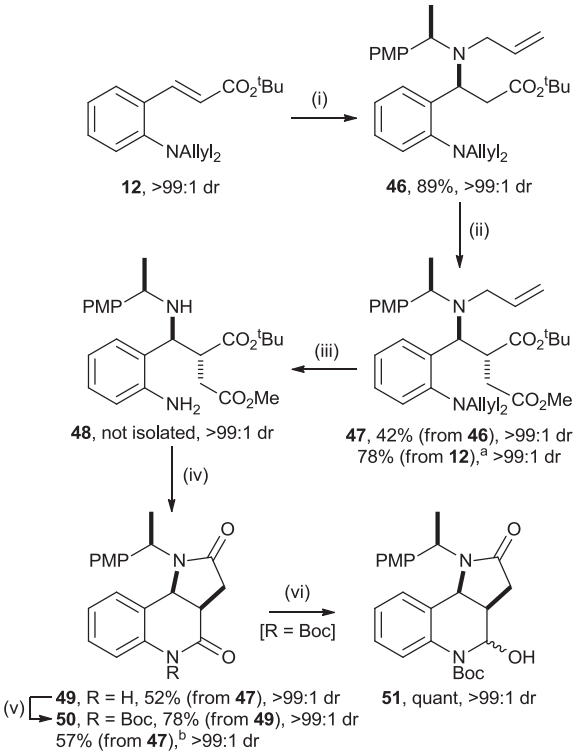
Scheme 8. Reagents and conditions: (i) $Pd(OAc)_2$, Xantphos, Et_3N, MeOH, 70 °C, 16 h; (ii) NaCN, DMSO, 90 °C, 16 h; (iii) $Pd(OH)_2/C$, H_2 (1 atm), HCl, MeOH, rt, 16 h.

In summary, our first generation synthetic route enabled the rapid and highly selective generation of the tricyclic molecular architecture required for the synthesis of (−)-martinellic acid **1**, although this approach suffered a number of drawbacks: (i) dibromination of the aromatic ring was also observed, (ii) methoxycarbonylation of the aryl bromide was incomplete and the product was isolated in low yield, (iii) the *N*-α-methylbenzyl group within **44** could not be deprotected by hydrogenolysis, and (iv) the *N*(5) atom participated in a cyclisation during attempted reduction of the nitrile group. It was hoped that issues (i), (ii) and (iv) could be addressed by maintaining an *N*(5)-Boc protecting group until the end of the synthesis, and it was thought that a differentially functionalised *N*-α-methylbenzyl group would allow deprotection without recourse to hydrogenolysis. Numerous derivatives of α-methylbenzylamine are commercially available as either enantiomer and have the advantage of being deprotected under a variety of conditions.[12] In particular, derivatives of α-methyl-*p*-methoxybenzylamine can be deprotected by treatment with acid,[13p] CAN,[29] or DDQ.[30] As it was ultimately desired to isolate **3** as the corresponding hydrochloride salt, following reports of the instability of the free base,[8a] a strategy was adopted in which the final steps would be nitrile hydrogenolysis followed by global *N*-Boc deprotection under acidic conditions.

2.4. Model studies: alternative synthetic strategy

Conjugate addition of lithium (*R*)-*N*-allyl-*N*-(α-methyl-*p*-methoxybenzyl)amide[31] to α,β-unsaturated ester **12** gave **46** in 89% yield and >99:1 dr. Deprotonation of **46** with LDA followed by addition of methyl bromoacetate gave **47** in >98:2 dr, and 42% yield and >99:1 dr after chromatographic purification. However, a superior yield of **47** was obtained when the two steps were run sequentially without purification of **46**; in this case **47** was isolated in 78% yield (from **12**) and >99:1 dr. N,N′-Deallylation of **47**, under the previously optimised conditions, gave **48** in >99:1 dr, and treatment of the crude reaction mixture with $PhCO_2H$ in PhMe at reflux resulted in cyclisation to give **49** in 52% yield. *N*-Boc protection of **49** upon treatment with Boc_2O and DMAP gave **50**, which was isolated in 78% yield and >99:1 dr after recrystallisation from PhMe. However, when the synthesis was repeated (without purification of either **48** or **49**), **50** was isolated in 57% overall yield (from **47**) for the three-step procedure (Scheme 9). The relative configuration within **50** was determined unambiguously by single crystal X-ray diffraction analysis (Fig. 8),[19,24] and the absolute (3a*R*,9b*S*,α*R*)-configuration within **50** was assigned by reference to the known (*R*)-configuration of the α-methyl-*p*-methoxybenzyl fragment; this analysis also confirmed the assigned configurations within **46**–**49**. Treatment of **50** with $LiAl(O^tBu)_3H$ in THF at 0 °C gave hemiaminal **51** [of undetermined configuration at C(4)] in quantitative yield and >99:1 dr (Scheme 9).

Attention was next turned to the olefination and in situ intramolecular aza-Michael addition of **51**. Treatment of **51** with excess phosphorane **38** (3.0 equiv) in PhMe at 80 °C proceeded within 72 h to give **52** as the sole product, although **52** was found to be inseparable from the remaining phosphorane **38** and Ph_3PO residues. It was therefore decided to explore the corresponding olefination protocol with phosphonate **54**, which it was hoped would be more readily separable from the reaction products. Reaction of **51** with 1.1 equiv of the anion derived from deprotonation of **54** with NaH produced the corresponding 3a,4-*syn*-diastereoisomer as the major product, giving a 76:24 mixture of **53** and **52**, which were isolated in 67 and 20% yield, respectively (Scheme 10). The conditions for this reaction were then screened, varying the concentration, temperature and number of equivalents of base used. Varying mixtures of **52** and **53** were observed, although despite these efforts the reaction could not be optimised further.



Scheme 9. Reagents and conditions: (i) lithium (*R*)-*N*-allyl-*N*-(α-methyl-*p*-methoxybenzyl)amide, THF, −78 °C, 2 h; (ii) LDA, THF, −78 °C, 1 h then methyl bromoacetate, −78 °C to rt, 16 h; (iii) $Pd(PPh_3)_4$, DMBA, CH_2Cl_2, 35 °C, 16 h; (iv) $PhCO_2H$, PhMe, reflux, 16 h; (v) Boc_2O, DMAP, Et_3N, CH_2Cl_2, 35 °C, 16 h; (vi) $LiAl(O^tBu)_3H$, THF, 0 °C, 1 h [[a]overall yield for the two-step procedure; [b]overall yield for three-step procedure; PMP=*p*-methoxyphenyl].

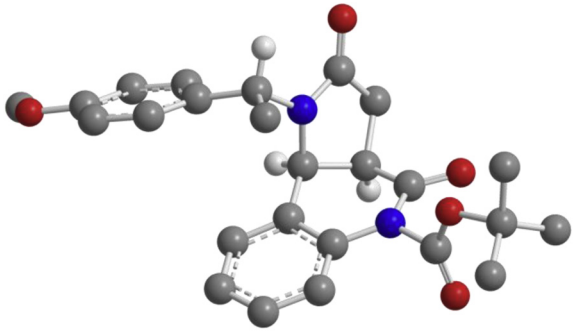
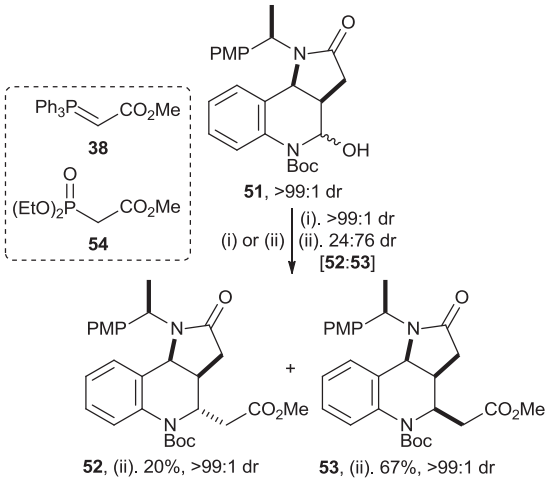


Fig. 8. X-ray crystal structure of **50** (selected H atoms are omitted for clarity).

Treatment of either **52** or **53** in MeOH at reflux for 36 h resulted in no loss of diastereoisomeric purity or decomposition, suggesting that the equilibration of either diastereoisomer (via an $E1_{cb}$-type process followed by intramolecular aza-Michael addition) requires the presence of a strong base. Indeed, treatment of **53** (>99:1 dr) with NaH (1.0 equiv) in THF at 0 °C to rt for 16 h gave a 57:43 mixture of **53** and **52**, which were isolated in 48 and 27% yield, respectively. Treatment of **52** (>99:1 dr) under the same conditions gave a 48:52 mixture of **52** and **53** (Scheme 11). In neither case was there any evidence of olefinic products in the ^1H NMR spectra of the crude reaction mixtures.[32] In summary, the reaction of **51** with phosphorane **38** proceeded to give the 3,4-*anti*-diastereoisomer exclusively. However, the synthetic utility of this reaction is

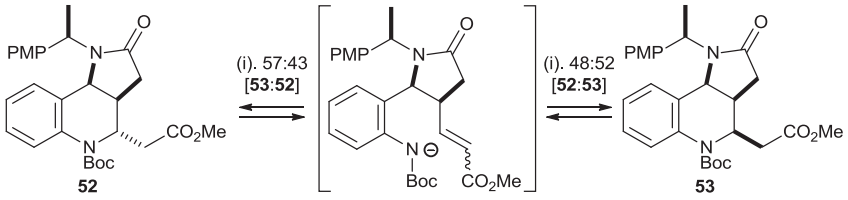


Scheme 10. Reagents and conditions: (i) **38**, PhMe, 80 °C, 72 h; (ii) **54**, NaH, THF, 0 °C, 2 h [PMP=*p*-methoxyphenyl].

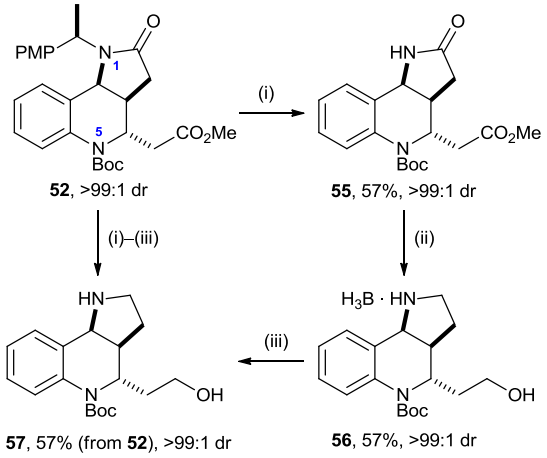
diminished by the difficulty in separating **52** from the reaction by-products. In contrast, the reaction of **51** with phosphonate **54** proceeds to give a 76:24 mixture of **53** and **52**. As these diastereoisomerically pure (>99:1 dr) samples of both **52** and **53** equilibrate in the presence of NaH to give approximately 1:1 mixtures, it is difficult to draw any firm conclusions about the diastereoselectivity of ring-closure with equilibration occurring in tandem.

As this methodology provides access to both C(4)-epimers in synthetically viable yields attention turned towards the elaboration of the 3a,4-*anti*-diastereoisomer **52** to an analogue of **3**, lacking only the methyl ester substituent on the aromatic ring. Treatment of **52** with CAN in $MeCN/H_2O$ gave **55** in 57% isolated yield and >99:1 dr, in addition to *p*-methoxyacetophenone, which was isolated in 65% yield after purification. Subsequent treatment of **55** with excess $BH_3\cdot THF$ gave a mixture of products, from which borane complex **56** was isolated in 57% yield and >99:1 dr. The identity of **56** was confirmed by ^{11}B NMR spectroscopic analysis (δ_B −14.9 ppm), the presence of characteristic B–H stretches in the IR spectrum of **56** (ν_{max}=2361, 2370 cm^{-1}), and by high-resolution mass spectrometry {HRMS (ESI^+) $C_{18}H_{29}BN_2NaO_3^+$ ([**56**+Na]$^+$) requires 355.2163; found 355.2162}. Decomplexation of **56** upon treatment with Pd/C in MeOH[33,34] proceeded to full conversion to give amine **57**. This simple decomplexation procedure was then applied to the crude material from the borane reduction step, and **57** was isolated in 57% overall yield (from **52**) and >99:1 dr (Scheme 12).

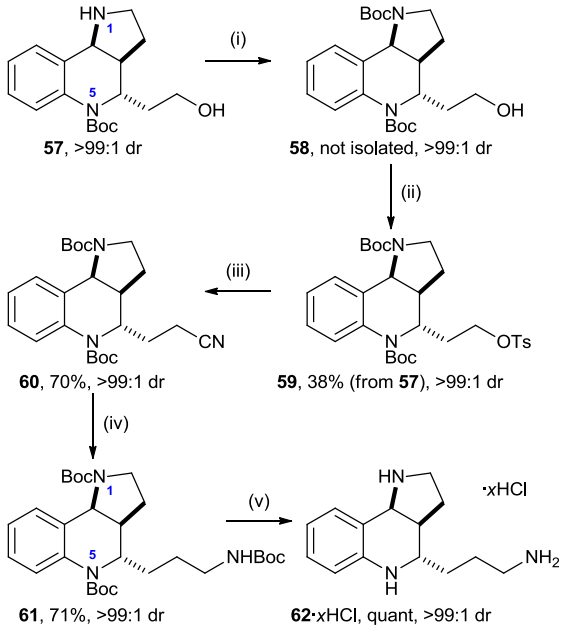
Efforts were next directed at the elaboration of **57** to **62**·*x*HCl. *N*-Boc protection of the *N*(1) atom within **57** gave **58** in >99:1 dr. The crude product was tosylated to give **59** in 38% overall yield (from **57**),[35] and treatment of **59** with NaCN in *N*-methyl-2-pyrrolidinone (NMP)[36] gave **60** as a single diastereoisomer (>99:1 dr) in 70% isolated yield. Reduction of the nitrile group within **60** and in situ *N*-Boc protection of the resultant primary amino group was achieved upon treatment of **60** with $NiCl_2\cdot 6H_2O$, $NaBH_4$ and Boc_2O,[37] which gave **61** in 71% isolated yield and >99:1 dr. Subsequent global N-deprotection of **61** with methanolic HCl gave **62**·*x*HCl (an analogue of **3**·*x*HCl, lacking only the methyl ester substituent on the aromatic ring) in quantitative yield (Scheme 13).[38] Modification of this route would enable the synthesis of **3**·*x*HCl, which could then be elaborated to (−)-martinellic acid **1** using literature conditions.[7a] It was envisaged that a C(8)-aryl bromide functionality could be maintained from the start of the synthesis and this functionality could be converted to a methyl ester upon methoxycarbonylation at a late stage.



Scheme 11. Reagents and conditions: (i) NaH (1.0 equiv), THF, 0 °C to rt, 16 h [PMP=*p*-methoxyphenyl].



Scheme 12. Reagents and conditions: (i) CAN, MeCN/H_2O (1:1), rt, 1 h; (ii) BH_3·THF, THF, reflux, 4 h; (iii) Pd/C, MeOH, rt, 16 h [PMP=*p*-methoxyphenyl].



Scheme 13. Reagents and conditions: (i) Boc_2O, Et_3N, DMAP, CH_2Cl_2, 35 °C, 16 h; (ii) TsCl, Et_3N, DMAP, CH_2Cl_2, 35 °C, 16 h; (iii) NaCN, NMP, 60 °C, 16 h; (iv) $NiCl_2·6H_2O$, $NaBH_4$, Boc_2O, MeOH, 0 °C to rt, 16 h; (v) HCl (1.25 M in MeOH), rt, 16 h.

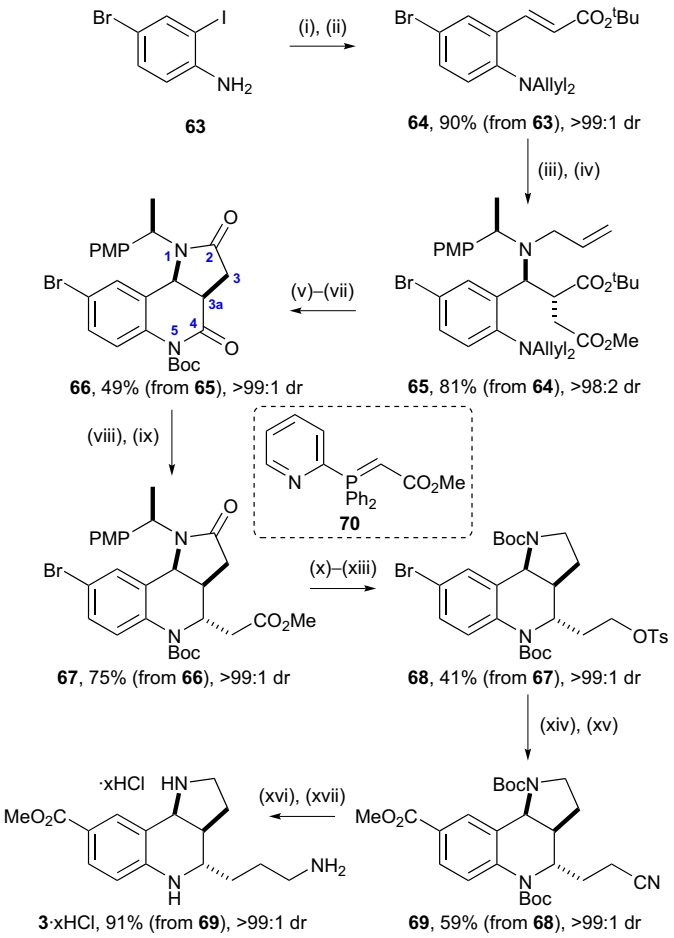
2.5. Asymmetric syntheses of (−)-martinellic acid and (−)-4-*epi*-martinellic acid

α,β-Unsaturated ester **64** was prepared in 90% yield and >99:1 dr upon Heck coupling of 2-iodo-4-bromoaniline **63**[39] with *tert*-butyl acrylate, followed by bis-*N*-allyl protection. Conjugate addition of lithium (*R*)-*N*-allyl-*N*-(α-methyl-*p*-methoxybenzyl)amide to **64** followed by alkylation with methyl bromoacetate gave **65** in 81% isolated yield (from **64**) and >98:2 dr. N-Deallylation of **65** followed by $PhCO_2H$-promoted ring-closure and subsequent *N*(5)-Boc protection gave **66** as a single diastereoisomer (>99:1 dr) in 49% yield (from **65**).[40] Chemoselective reduction of **66** with $LiAl(O^tBu)_3H$ followed by reaction with phosphorane **70**[41,42] gave **67** as the sole reaction product (>99:1 dr), and **67** was subsequently isolated in 75% yield (from **66**) and >99:1 dr.[40] N(1)-Deprotection of **67** upon treatment with CAN, reduction with BH_3, *N*(1)-Boc protection, and tosylation gave **68** in 41% overall yield (from **67**). Treatment of **68** with NaCN in NMP, followed by methoxycarbonylation gave **69** as a single diastereoisomer (>99:1 dr) in 59% yield (from **68**). Subsequent reduction of the nitrile group within **69**, then deprotection of the three *N*-Boc groups gave **3**·*x*HCl in 91% yield (from **69**) and >99:1 dr (Scheme 14), completing a formal synthesis of (−)-martinellic acid **1** in 6.0% yield over 17 steps from commercially available starting materials. The spectroscopic data for our sample of **3**·*x*HCl were in excellent agreement with literature values, as communicated previously.[15]

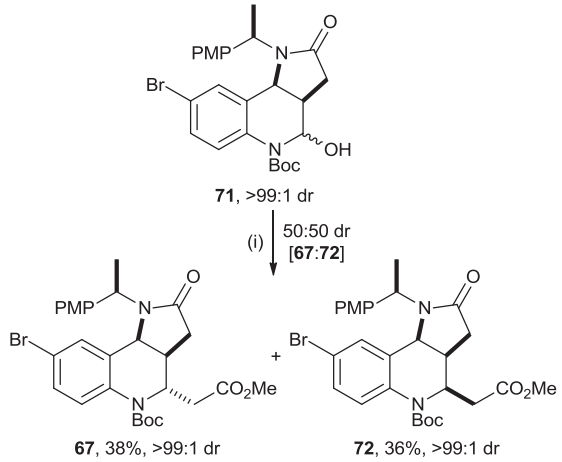
A synthesis of the C(4)-epimer of **3**·*x*HCl was targeted next. Under optimised conditions, treatment of **71** [which was obtained upon reduction of **66** with $LiAl(O^tBu)_3H$] with phosphonate **54** (1.1 equiv) and NaH in THF at 0 °C for 2 h gave a 50:50 mixture of C(4)-epimers **67** and **72**, which were isolated in 38 and 36% yield, respectively, as single diastereoisomers (>99:1 dr) after chromatographic purification (Scheme 15).

Elaboration of the 3a,4-*syn*-diastereoisomer **72**, following an analogous series of steps to those used for the synthesis of **3**·*x*HCl, gave **79**·*x*HCl in 18% overall yield: treatment of **72** with CAN in MeCN/H_2O gave **73**, which was reduced by treatment with BH_3·THF at reflux to give **74** in 53% yield over three steps (from **72**). *N*(1)-Boc protection of **74** followed by O-tosylation gave **75** in 63% yield over two steps (from **74**). Displacement of the tosylate group within **75** with NaCN in NMP gave **76** in 87% yield. Repeated methoxycarbonylation of **76** using the $Pd(OAc)_2$/Xantphos catalyst system gave **77** in 74% isolated yield and >99:1 dr. Reduction of the nitrile functionality within **77** by hydrogenation with Ni_2B and H_2 formed in situ from $NiCl_2·6H_2O$ and $NaBH_4$, and trapping of the primary amine with Boc_2O gave **78** in 83% yield. Global N-deprotection of **78** was achieved by treatment with methanolic HCl for 6 h at rt, which gave **79**·*x*HCl in quantitative yield and >99:1 dr (Scheme 16). The spectroscopic properties of (+)-**79**·*x*HCl were in good agreement with those previously reported for its antipode {$[\alpha]_D^{20}$ +93.7 (*c* 0.35, MeOH); lit.[9c] for enantiomer $[\alpha]_D^{16}$ −73.7 (*c* 0.34, MeOH)}.

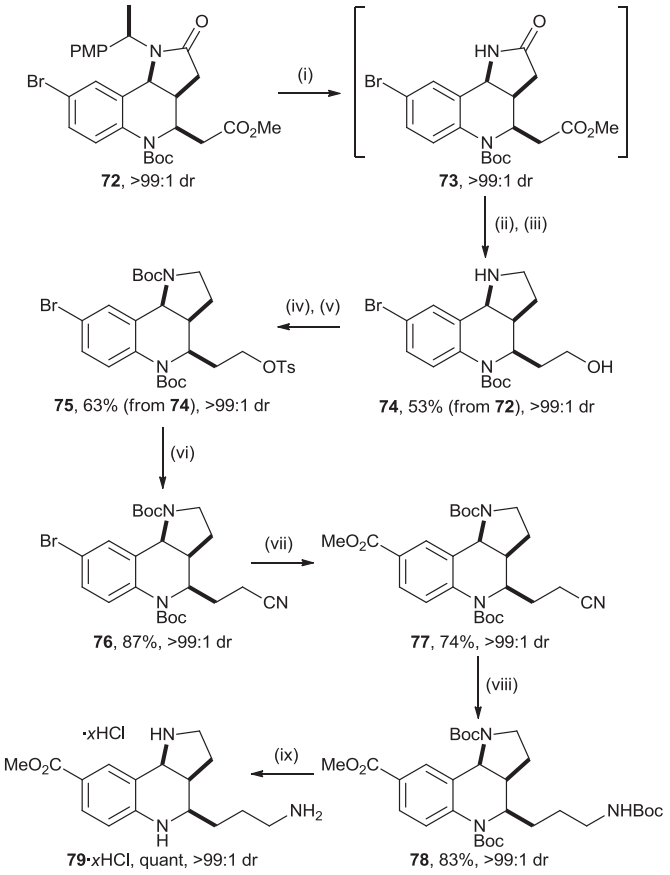
Conversion of **3**·*x*HCl and **79**·*x*HCl into (−)-martinellic acid **1** and (−)-4-*epi*-martinellic acid **83**, respectively, was achieved according to a literature procedure:[7a] in our hands, application of this protocol to **3**·*x*HCl gave **1**·*x*TFA in 22% overall yield, as communicated previously (Scheme 17).[15] The spectroscopic data for this sample of (−)-martinellic acid **1**·*x*TFA, including its specific rotation {$[\alpha]_D^{20}$ −118 (*c* 0.3, MeOH)}, were consistent with literature data {lit.[1] for sample isolated from natural source $[\alpha]_D$ −8.5 (*c* 0.01, MeOH); lit.[7a] $[\alpha]_D^{20}$ −112.7 (*c* 0.31 in MeOH); lit.[7b] $[\alpha]_D^{29}$ −164.3 (*c* 0.14, MeOH); lit.[7c] $[\alpha]_D^{23}$ −164.8 (*c* 0.33, MeOH)}. Overall, (−)-martinellic acid **1** was isolated as its trifluoroacetate salt in 20 steps and



Scheme 14. Reagents and conditions: (i) $Pd(OAc)_2$, P(*o*-Tol)$_3$, *tert*-butyl acrylate, Et_3N, MeCN, 70 °C, 16 h; (ii) K_3PO_4, allyl iodide, acetone, reflux, 48 h; (iii) lithium (*R*)-*N*-allyl-*N*-(α-methyl-*p*-methoxybenzyl)amide, THF, −78 °C, 2 h; (iv) LDA, THF, −78 °C, 1 h then MeO_2CCH_2Br, −78 °C to rt, 16 h; (v) $Pd(PPh_3)_4$, DMBA, CH_2Cl_2, 35 °C, 16 h; (vi) $PhCO_2H$, PhMe, reflux, 16 h; (vii) Boc_2O, DMAP, CH_2Cl_2, 35 °C, 16 h; (viii) $LiAl(O^tBu)_3H$, THF, 0 °C, 1 h; (ix) **70**, PhMe, 80 °C, 72 h; (x) CAN, MeCN/H_2O (1:1), rt, 1 h; (xi) BH_3·THF, reflux, 3 h then MeOH, reflux, 48 h; (xii) Boc_2O, Et_3N, DMAP, CH_2Cl_2, 35 °C, 5 h; (xiii) TsCl, Et_3N, DMAP, CH_2Cl_2, 35 °C, 16 h; (xiv) NaCN, NMP, 60 °C, 16 h; (xv) CO (1 atm), $Pd(OAc)_2$, Xantphos, Et_3N, MeOH, 70 °C, 48 h; (xvi) $NiCl_2·6H_2O$, $NaBH_4$, Boc_2O, MeOH, 0 °C, 1 h; (xvii) HCl, MeOH, rt, 6 h [PMP=*p*-methoxyphenyl].



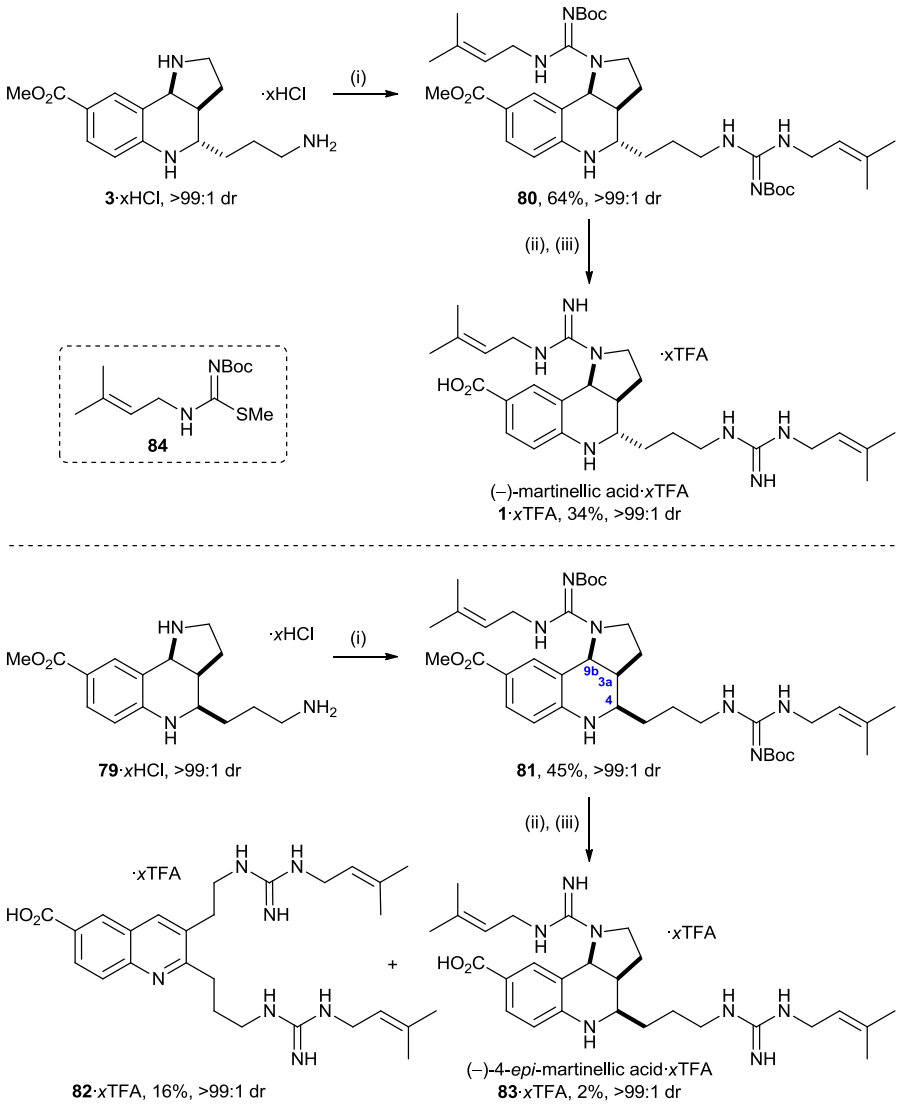
Scheme 15. Reagents and conditions: (i) **54**, NaH, THF, 0 °C, 2 h [PMP=*p*-methoxyphenyl].



Scheme 16. Reagents and conditions: (i) CAN, MeCN/H_2O (2:1), rt, 1 h; (ii) BH_3·THF, THF, reflux, 4 h; (iii) MeOH, reflux, 48 h; (iv) Boc_2O, Et_3N, DMAP, CH_2Cl_2, 35 °C, 16 h; (v) TsCl, Et_3N, DMAP, CH_2Cl_2, 35 °C, 16 h; (vi) NaCN, NMP, 60 °C, 16 h; (vii) $Pd(OAc)_2$, Xantphos, Et_3N, MeOH, CO (1 atm), 70 °C, 48 h; (viii) $NiCl_2·6H_2O$, $NaBH_4$, Boc_2O, MeOH, 0 °C, 1 h; (ix) HCl (1.25 M in MeOH), rt, 6 h [PMP=*p*-methoxyphenyl].

1.3% yield from commercially available starting materials. However, in the epimeric series, coupling of **79**·*x*HCl (>99:1 dr) with thiourea **84**, Et_3N and $AgNO_3$ in MeCN/MeOH gave **81** in 45% yield and >99:1 dr after chromatographic purification. Hydrolysis of **81** with NaOH in H_2O/MeOH, followed by global *N*-Boc deprotection gave a mixture of products, including **82**·*x*TFA and **83**·*x*TFA, which were isolated in 16 and 2% yield, respectively (Scheme 17). Quinoline **82** could potentially arise from either oxidation of the *N*(5) atom, followed by aromatisation, or elimination across the C(3a)–C(9b) bond, followed by oxidation. Although it is notable that the C(4)–H bond is relatively exposed for **81** (as opposed to **80**), it is unclear why there is such a difference in reactivity between these two epimers, and why this fragmentation pathway was not observed for any precursors to **81**.[43]

Application of alternative literature conditions for the introduction of the guanidine moieties was attempted next, following the procedure reported by Snider et al.[8a,44] Treatment of both **3**·*x*HCl and **79**·*x*HCl with BrCN gave bis-cyanamides **85** and **87**, respectively, then a solution of prenylamine in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) was added, which gave **86** and **88**. Hydrolysis of **86** and **88** with 0.15 M aq NaOH at reflux in MeOH proceeded to give (−)-martinellic acid **1** and (−)-4-*epi*-martinellic acid **83**, which were isolated as the corresponding trifluoroacetate salts in 6 and 3% overall yield (from **3**·*x*HCl and **79**·*x*HCl), respectively, after purification via reverse phase HPLC (Scheme 18). In both cases, ^1H NMR spectroscopic analysis of the crude reaction mixtures indicated that quinoline by-products had not been



Scheme 17. Reagents and conditions: (i) **84**, $AgNO_3$, Et_3N, MeCN/MeOH (2:1), 40 °C, 16 h; (ii) NaOH (0.2 M aq), MeOH, reflux, 16 h; (iii) TFA, anisole, CH_2Cl_2, rt, 16 h [PMP=*p*-methoxyphenyl].

formed; this route therefore offers a superior yield of (−)-4-*epi*-martinellic acid **83**·*x*TFA to that obtained using Ma's procedure.

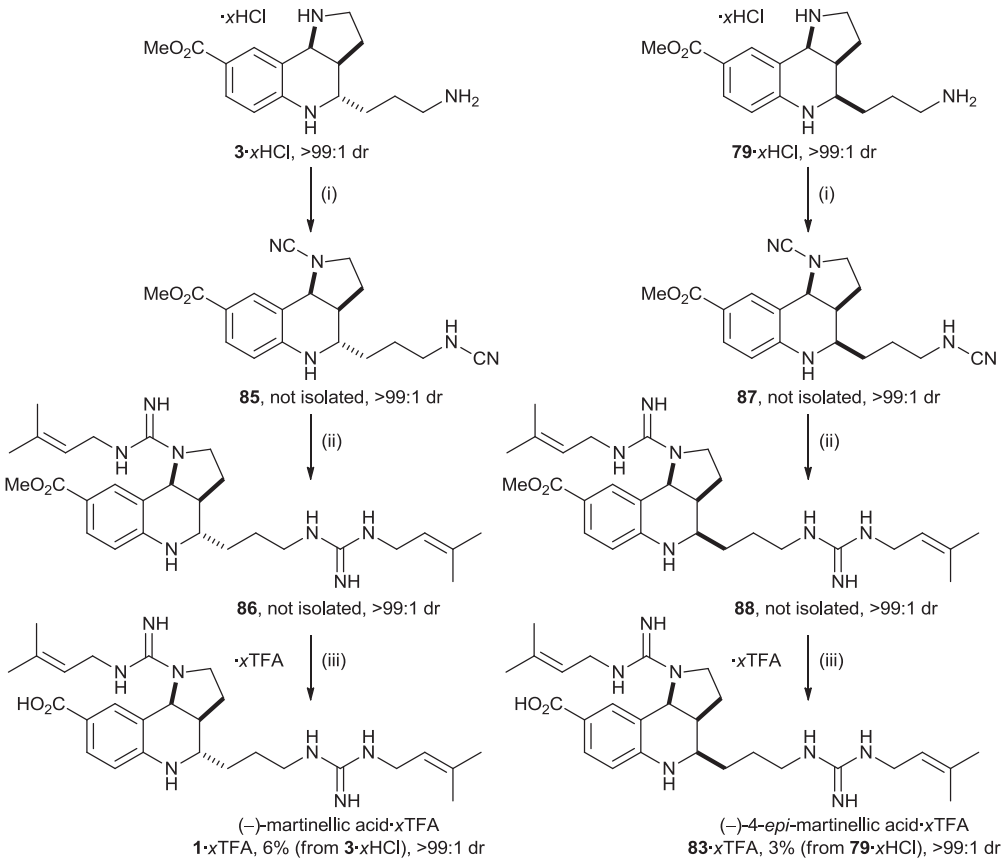
3. Conclusion

In conclusion, a diastereodivergent strategy for the asymmetric syntheses of both (−)-martinellic acid and (−)-4-*epi*-martinellic acid has been developed. The conjugate addition of lithium (*R*)-*N*-allyl-*N*-(α-methyl-*p*-methoxybenzyl)amide to *tert*-butyl (*E*)-3-[2′-(*N*,*N*-diallylamino)-5′-bromophenyl]propenoate and alkylation of the resultant β-amino ester have been used as the key steps to install the C(9b) and C(3a) stereogenic centres, respectively. Subsequent cyclisation to the corresponding dihydroquinolin-2-one and reduction of the C(4) carbonyl group was followed by two diastereodivergent procedures for the introduction of the C(4)-side chain via olefination and concomitant intramolecular Michael addition, which gave both C(4)-epimers of this tricyclic molecular architecture as single diastereoisomers (>99:1 dr). Subsequent elaboration of these templates provided access to (−)-martinellic acid in 1.3% overall yield and, for the first time, (−)-4-*epi*-martinellic acid in 0.1% overall yield, from commercially available starting materials in each case.

4. Experimental

4.1. General experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs et al.[45] BuLi was purchased as a solution in hexanes and titrated against diphenylacetic acid before use. All other reagents were used as supplied without prior purification. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), 1% aq $KMnO_4$ or Dragendorff's reagent. Flash column chromatography was performed on Kieselgel 60 silica. Melting points are uncorrected. Specific rotations are reported in



Scheme 18. Reagents and conditions: (i) BrCN, $NaHCO_3$, MeOH, 0 °C, 1 h; (ii) prenylamine, HFIP, 110 °C, 5 days; (iii) NaOH (0.15 M aq), MeOH, reflux, 16 h.

10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded using an ATR module. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded in the deuterated solvent stated. Spectra were recorded at rt unless otherwise stated. The field was locked by external referencing to the relevant deuteron resonance. $^1H-^1H$ COSY, $^1H-^{13}C$ HMQC, and $^1H-^{13}C$ HMBC analyses were used to establish atom connectivity. Accurate mass measurements were run on a TOF spectrometer internally calibrated with polyalanine.

4.2. General procedure 1: conjugate addition of lithium amides to α,β-unsaturated esters

BuLi was added to a solution of the requisite amine (1.6 equiv) in THF at −78 °C and the resultant mixture was stirred at −78 °C for 30 min. A solution of the requisite α,β-unsaturated ester (1.0 equiv) in THF at −78 °C was added via cannula and the resultant mixture was stirred at −78 °C for 2 h. Satd aq NH_4Cl was then added and the reaction mixture was allowed to warm to rt. The organic phase was washed with 10% aq citric acid (×2) and the combined aqueous layers were extracted with Et_2O. The combined organic layers were washed sequentially with satd aq $NaHCO_3$ and brine, then dried and concentrated in vacuo.

4.3. General procedure 2: β-amino ester alkylation

BuLi was added to a solution of $^iPr_2NH$ (1.5 equiv) in THF at 0 °C. The resultant mixture was stirred for 15 min at 0 °C then cooled to −78 °C and stirred at −78 °C for 30 min. A solution of the requisite β-amino ester (1.0 equiv) in THF at −78 °C was then added via cannula and the resultant mixture was stirred at −78 °C for 1 h. The requisite electrophile (3.0 equiv) was then added slowly and the reaction mixture was allowed to warm to rt over 16 h. Satd aq NH_4Cl was then added. The reaction mixture was washed with 10% aq citric acid (×2) and the combined aqueous layers were extracted with Et_2O. The combined organic extracts were then washed sequentially with satd aq $NaHCO_3$ and brine, then dried and concentrated in vacuo.

4.4. General procedure 3: N-deallylation

A solution of the requisite substrate (1.0 equiv) in CH_2Cl_2 and DMBA (3.0 equiv per allyl group) was thoroughly purged with argon for ~10 min. $Pd(PPh_3)_4$ was then added in one portion under a stream of argon. The resultant mixture was stirred at 35 °C (in the dark) for 16 h then concentrated in vacuo. The residue was dissolved in Et_2O and the resultant solution was washed with satd aq K_2CO_3 (×2). The combined aqueous layers were then extracted with Et_2O and the combined organic extracts were dried and concentrated in vacuo.

4.5. General procedure 4: cyclisation of aniline derivatives

$PhCO_2H$ was added to a solution of the requisite substrate (1.0 equiv) in either THF or PhMe, as stated. The resultant mixture was heated at 50 °C or reflux for either 16 or 72 h, as stated. The reaction mixture was then concentrated in vacuo. The residue was dissolved in CH_2Cl_2 and the resultant solution was washed with satd aq K_2CO_3 (×2). The combined aqueous layers were then extracted with CH_2Cl_2 and the combined organic extracts were dried and concentrated in vacuo.

4.6. General procedure 5: oxidative N-debenzylation with CAN

A solution of CAN (3.0 equiv) in H_2O (10 mL mmol^{-1} of substrate) was added dropwise to a solution of the requisite substrate (1.0 equiv) in MeCN (10 mL mmol^{-1} of substrate) and the resultant mixture was stirred at rt for 1 h. MeCN was then removed in vacuo and the resultant mixture was partitioned between brine and $CHCl_3$/IPA (3:1). The organic layer was washed with brine (×2) and the combined aqueous layers were extracted with $CHCl_3$/IPA (3:1, ×5). The combined organic extracts were then dried and concentrated in vacuo.

4.7. General procedure 6: palladium-catalysed methoxycarbonylation

A flask containing the requisite substrate (1.0 equiv) was evacuated using a vacuum manifold and was backfilled with N_2 (×3). The requisite phosphine ligand and palladium source were added sequentially. Degassed Et_3N then degassed MeOH were added via syringe. The resultant mixture was stirred at rt and the apparatus was carefully evacuated using a vacuum manifold, and was then backfilled with N_2; the process was then repeated (×2). The reaction mixture was purged for ~30 min with CO, then the apparatus was carefully evacuated using a vacuum manifold, and was then backfilled with CO; the process was then repeated (×2). The resultant mixture was submerged in a preheated oil bath at 70 °C and was vigorously stirred under CO for 16 h. The reaction mixture was then filtered through Celite® (eluent MeOH/Et_3N, 100:1) and concentrated in vacuo.

4.8. *tert*-Butyl (*E*)-3-(2′-aminophenyl)propenoate 11

P(*o*-Tol)$_3$ (3.77 g, 12.4 mmol), Et_3N (32.0 mL), *tert*-butyl acrylate (18.4 mL, 125 mmol) and $Pd(OAc)_2$ (1.28 g, 5.70 mmol) were added sequentially to a solution of **10** (25.0 g, 114 mmol) in degassed MeCN (250 mL) under an argon atmosphere, and the resultant solution was stirred at 70 °C for 16 h. The reaction mixture was then allowed to cool to rt and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (300 mL) and the resultant solution was washed with H_2O (2×200 mL). The aqueous layer was extracted with CH_2Cl_2 (2×150 mL), and the combined organic extracts were then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:1) gave **11** as a yellow solid (21.5 g, 85%, >99:1 dr); $C_{13}H_{17}NO_2$ requires C, 71.2; H, 7.8; N, 6.4%; found: C, 71.2; H, 7.8; N, 6.4%; mp 76–77 °C; ν_{max} (ATR) 1695 (C=O); δ_H (400 MHz, $CDCl_3$) 1.54 (9H, s, CMe_3), 3.97 (2H, br s, NH_2), 6.29 (1H, d, *J* 15.7, C(2)*H*), 6.70 (1H, dd, *J* 8.2, 1.0, *Ar*), 6.74–6.78 (1H, m, *Ar*), 7.14–7.18 (1H, m, *Ar*), 7.36–7.38 (1H, m, *Ar*), 7.74 (1H, d, *J* 15.7, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 28.2 (CMe_3), 80.5 (CMe_3), 116.7, 119.1 (*Ar*), 120.3 (*C*(2)), 128.1, 130.9 (*Ar*), 139.0 (*C*(3)), 139.0 (*C*(1′)), 145.1 (*C*(2′)), 166.6 (*C*(1)); *m*/*z* (ESI$^+$) 220 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{18}NO_2^+$ ([M+H]$^+$) requires 220.1332; found 220.1330.

4.9. *tert*-Butyl (*E*)-3-(2′-*N*,*N*-diallylaminophenyl)propenoate 12

Method A: Allyl iodide (1.87 mL, 20.0 mmol) was added to a mixture of K_3PO_4 (18.0 g, 84.6 mmol) and **11** (6.07 g, 27.7 mmol, >99:1 dr) in acetone (50 mL) and the resultant mixture was heated at reflux for 48 h. The reaction mixture was allowed to cool to rt then diluted with H_2O (50 mL) and Et_2O (100 mL). The aqueous layer was extracted with Et_2O (2×50 mL) and the combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 95:5) gave **12** as a yellow oil (2.00 g, 73%, >99:1 dr); $C_{19}H_{25}NO_2$ requires C, 76.2; H, 8.4; N, 4.7%; found: C, 76.05; H, 8.4; N, 4.6%; ν_{max} (ATR) 1708 (C=O); δ_H (400 MHz, $CDCl_3$) 1.55 (9H, s, CMe_3), 3.65 (4H, d, N(CH_2CH=CH$_2$)$_2$), 5.12–5.21 (4H, m, N(CH$_2$CH=CH_2)$_2$), 5.77–5.87 (2H, m, N(CH$_2$CH=CH$_2$)$_2$), 6.31 (1H, d, *J* 16.2, C(2)*H*), 7.00–7.05 (2H, m, *Ar*), 7.25–7.31 (1H, m, *Ar*), 7.51–7.55 (1H, m, *Ar*), 8.04 (1H, d, *J* 16.2, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 28.2 (CMe_3), 56.1 (N(CH_2CH=CH$_2$)$_2$), 80.2 (CMe_3), 117.6 (N(CH$_2$CH=CH_2)$_2$), 119.6 (*C*(2)), 121.5, 122.6, 127.8 (*Ar*), 129.7 (*C*(1′)), 129.8 (*Ar*), 134.6 (N(CH$_2$CH=CH$_2$)$_2$), 141.4 (*C*(3)), 150.8 (*C*(2′)), 166.7 (*C*(1)); *m*/*z* (ESI$^+$) 300 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{26}NO_2^+$ ([M+H]$^+$) requires 300.1958; found 300.1967.

Method B—step 1: P(*o*-Tol)$_3$ (725 mg, 2.38 mmol), Et_3N (33.1 mL, 238 mmol), *tert*-butyl acrylate (19.2 mL, 131 mmol) and $Pd(OAc)_2$ (267 mg, 1.19 mmol) were added sequentially to a solution of **10** (26.0 g, 119 mmol) in degassed MeCN (300 mL) under an argon atmosphere, and the resultant solution was stirred at 70 °C for 16 h. The reaction mixture was then allowed to cool to rt and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (300 mL) and the resultant solution was washed with H_2O (2×200 mL). The aqueous layer was extracted with CH_2Cl_2 (2×150 mL), and the combined organic extracts were then dried and concentrated in vacuo to give **11** (26.0 g, >99:1 dr).

Method B—step 2: Allyl iodide (27.0 mL, 298 mmol) was added to a solution of K_3PO_4 (76.0 g, 357 mmol) and **11** (26.0 g, >99:1 dr) in acetone (250 mL) and the resultant mixture was heated at reflux for 48 h. The reaction mixture was allowed to cool to rt then diluted with H_2O (100 mL) and Et_2O (200 mL). The aqueous layer was extracted with Et_2O (2×100 mL) and the combined organic extracts were then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 92:8) gave **12** as a yellow oil (31.6 g, 89% from **10**, >99:1 dr).

4.10. *tert*-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl) amino]-3-(2′-*N*,*N*-diallylaminophenyl)propanoate 13

Following *general procedure 1*, BuLi (2.25 M in hexanes, 16.9 mL, 38.0 mmol), (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine[12] (8.57 g, 25.4 mmol, >99:1 er) and **12** (7.61 g, 25.4 mmol, >99:1 dr) were reacted in THF (300 mL) to give **13** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave **13** as a yellow oil (12.6 g, 97%, >99:1 dr); $C_{34}H_{42}N_2O_2$ requires C, 80.0; H, 8.3; N, 5.5%; found C, 79.8; H, 8.1; N, 5.45%; $[\alpha]_D^{25}$ −9.5 (*c* 1.1, $CHCl_3$); ν_{max} (ATR) 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 1.28 (9H, s, CMe_3), 1.33 (3H, d, *J* 6.8, C(α)*Me*), 2.45 (1H, dd, *J* 15.5, 6.6, C(2)H_A), 2.68 (1H, dd, *J* 15.5, 7.6, C(2)H_B), 3.52 (2H, dd, *J* 14.2, 6.3, N(CH_AH$_B$CH=CH$_2$)$_2$), 3.61 (2H, dd, *J* 14.2, 6.7, N(CH$_A$H$_B$CH=CH$_2$)$_2$), 3.74 (1H, d, *J* 15.1, NCH_AH$_B$Ph), 3.86 (1H, d, *J* 15.1, NCH$_A$H$_B$Ph), 3.98 (1H, q, *J* 6.8, C(α)*H*), 5.08–5.24 (5H, m, C(3)*H*, N(CH$_2$CH=CH_2)$_2$), 5.75–5.90 (2H, m, N(CH$_2$CH=CH$_2$)$_2$), 7.07–7.37 (13H, m, *Ar*, *Ph*), 7.56 (1H, d, *J* 7.3, *Ar*); δ_C (100 MHz, $CDCl_3$) 14.4 (C(α)*Me*), 27.9 (CMe_3), 40.2 (*C*(2)), 49.9 (NCH$_2$Ph), 53.6 (*C*(3)), 56.8 (*C*(α)) 57.0 (N(CH$_2$CH=CH$_2$)$_2$), 80.0 (CMe_3), 117.6 (N(CH$_2$CH=CH$_2$)$_2$), 123.6, 124.0, 126.1, 126.5, 127.1, 127.8, 127.8, 127.9, 128.1, 129.0 (*Ar*, *Ph*), 135.0 (N(CH$_2$CHCH$_2$)$_2$), 139.3, 142.9, 144.3, 149.9 (*C*(1′), *C*(2′), *i*-*Ph*), 171.5 (*C*(1)); *m*/*z* (ESI$^+$) 511 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{34}H_{43}N_2O_2^+$ ([M+H]$^+$) requires 511.3319; found 511.3315.

4.11. *tert*-Butyl (2*R*,3*S*,α*R*)-2-(cyanomethyl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(2″-*N*,*N*-diallylaminophenyl)propanoate 14

Following *general procedure 2*, ^{i}Pr$_2$NH (0.43 mL, 3.09 mmol), BuLi (2.3 M in hexanes, 1.34 mL, 3.09 mmol), **13** (1.05 g, 2.06 mmol, >99:1 dr) and bromoacetonitrile (0.43 mL, 6.18 mmol) were reacted in THF (20 mL) to give **14** in 80:20 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O/Et_3N, 89:11:1) gave **14** as a yellow oil (765 mg, 67%, >99:1 dr); $[\alpha]_D^{25}$ −8.7

(c 1.9, $CHCl_3$); ν_{max} (ATR) 2978, 2933, 2821 (C–H), 2249 (C≡N), 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 1.20 (3H, d, J 6.6, C(α)*Me*), 1.60 (9H, s, C*Me*$_3$), 2.19 (1H, dd, J 16.4, 3.4, C(1′)H_A), 2.38 (1H, dd, J 16.4, 11.5, C(1′)H_B), 3.40 (1H, app td, J 11.5, 3.4, C(2)*H*), 3.52–3.68 (5H, m, NCH_AH$_B$Ph, N(CH_2CH=CH$_2$)$_2$), 3.84 (1H, d, J 14.4, NCH$_A$$H_B$Ph), 4.19 (1H, q, J 6.6, C(α)*H*), 5.13–5.25 (5H, m, C(3)*H*, N(CH$_2$CH=CH_2)$_2$), 5.77–5.90 (2H, m, N(CH$_2$C*H*=CH$_2$)$_2$), 7.07–7.39 (14H, m, *Ar*, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.3 (C(α)*Me*), 19.1 (*C*(1′)), 28.2 (C*Me*$_3$), 46.9 (*C*(2)), 51.6 (NCH$_2$Ph), 57.5 (N(*C*H$_2$CH=CH$_2$)$_2$), 57.7, 57.8 (*C*(3), *C*(α)), 82.4 (*C*Me$_3$), 117.7 (*C*(2′)), 118.8 (N(CH$_2$CH=*C*H$_2$)$_2$), 124.6, 125.2, 126.3, 126.5, 127.6, 128.3, 128.4, 128.8, 129.2, 133.6, 134.0, 140.9, 143.9, 151.5 (*Ar*, *Ph*, N(CH$_2$CH=CH$_2$)$_2$), 172.1 (*C*(1)); m/z (ESI$^+$) 572 ([M+Na]$^+$, 100%), 550 ([M+H]$^+$, 25%); HRMS (ESI$^+$) $C_{36}H_{43}N_3NaO_2^+$ ([M+Na]$^+$) requires 572.3247; found 572.3240.

4.12. *tert*-Butyl (2*R*,3*S*,α*R*)-2-(2′-*tert*-butoxy-2′-oxoethyl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(2″-*N*,*N*-diallylaminophenyl)propanoate 15

Following *general procedure 2*, ^{i}Pr$_2$NH (4.25 g, 20.2 mmol), BuLi (1.6 M in hexanes, 18.3 mL, 29.3 mmol), **13** (10.3 g, 20.2 mmol, >99:1 dr) and *tert*-butyl bromoacetate (9.85 g, 50.5 mmol) were reacted in THF (300 mL) to give **15** in >95:5 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et$_2$O, 5:1) gave **15** as a yellow oil (16.3 g, >99:1 dr, quant); $C_{40}H_{52}N_2O_4$ requires C, 76.9; H, 8.4; N, 4.5%; found C, 76.7; H, 8.4; N, 4.4%; $[\alpha]_D^{25}$ −9.6 (c 1.0, $CHCl_3$); ν_{max} (ATR) 3004, 2977, 2933 (C–H), 1731 (C=O), 1642, 1596 (C=C); δ_H (400 MHz, $CDCl_3$) 1.19 (3H, d, J 6.6, C(α)*Me*), 1.38 (9H, s, C*Me*$_3$), 1.51 (9H, s, C*Me*$_3$), 2.13 (1H, dd, J 15.4, 2.8, C(1′)H_A), 2.37 (1H, dd, J 15.4, 11.4, C(1′)H_B), 3.44–3.69 (6H, m, C(2)*H*, N(CH_2CH=CH$_2$)$_2$, NCH_AH$_B$Ph), 3.92 (1H, d, J 14.7, NCH$_A$$H_B$Ph), 4.23 (1H, q, J 6.6, C(α)*H*), 5.08–5.22 (5H, m, C(3)*H*, N(CH$_2$CH=CH_2)$_2$), 5.71–5.86 (2H, m, N(CH$_2$C*H*=CH$_2$)$_2$), 6.95–7.42 (14H, m, *Ar*, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.2 (C(α)*Me*), 28.0, 28.1 (2×C*Me*$_3$), 37.4 (*C*(1′)), 46.4 (*C*(2)), 51.2 (NCH$_2$Ph), 57.0 (N(CH$_2$CH=CH$_2$)$_2$), 57.6 (*C*(α)), 58.1 (*C*(3)), 80.8, 80.5 (2×CMe$_3$), 118.3 (N(CH$_2$CH=*C*H$_2$)$_2$), 124.1, 124.4, 125.8, 126.1, 127.3, 127.3, 127.6, 128.5, 128.7, 129.5, 134.2, 134.3, 141.5, 143.9, 151.4 (N(CH$_2$CH=CH$_2$)$_2$, *Ar*, *Ph*), 171.0, 173.9 (*C*(1), *C*(2′)); m/z (ESI$^+$) 647 ([M+Na]$^+$, 100%), 625 ([M+H]$^+$, 73%); HRMS (ESI$^+$) $C_{40}H_{53}N_2O_4^+$ ([M+H]$^+$) requires 625.4000; found 625.3999.

4.13. *tert*-Butyl (2*R*,3*S*,α*R*)-2-(2′-methoxy-2′-oxoethyl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(2″-*N*,*N*-diallylaminophenyl)propanoate 16

Following *general procedure 2*, ^{i}Pr$_2$NH (0.44 mL, 3.14 mmol), BuLi (2.3 M in hexanes, 1.37 mL, 3.14 mmol), **13** (1.07 g, 2.09 mmol, >99:1 dr) and methyl bromoacetate (0.59 mL, 6.27 mmol) were reacted in THF (20 mL) to give **16** in >95:5 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et$_2$O/Et$_3$N, 89:11:1) gave **16** as a yellow oil (1.00 g, 82%, >99:1 dr); $C_{37}H_{46}N_2O_4$ requires C, 76.3; H, 8.0; N, 4.8%; found C, 76.3; H, 8.1; N, 4.8%; $[\alpha]_D^{25}$ −16.2 (c 2.0, $CHCl_3$); ν_{max} (ATR) 3062, 3027, 2977 (C–H), 1741 (C=O), 1666, 1642, 1597, 1485 (C=C); δ_H (400 MHz, $CDCl_3$) 1.19 (3H, d, J 6.6, C(α)*Me*), 1.49 (9H, s, C*Me*$_3$), 2.21 (1H, dd, J 15.4, 2.8, C(1′)H_A), 2.46 (1H, dd, J 15.4, 11.5, C(1′)H_B), 3.45–3.68 (9H, m, C(2)*H*, O*Me*, N(CH_2CH=CH$_2$)$_2$, NCH_AH$_B$Ph), 3.93 (1H, d, J 14.4, NCH$_A$$H_B$Ph), 4.22 (1H, q, J 6.6, C(α)*H*), 5.10–5.20 (5H, m, C(3)*H*, N(CH$_2$CH=CH_2)$_2$), 5.72–5.85 (2H, m, N(CH$_2$C*H*=CH$_2$)$_2$), 6.96–7.41 (14H, m, *Ar*, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.8 (C(α)*Me*), 28.1 (C*Me*$_3$), 36.0 (*C*(1′)), 46.3 (*C*(2)), 51.3 (NCH_2Ph), 51.6 (O*Me*), 57.0 (N(*C*H$_2$CH=CH$_2$)$_2$), 57.4 (*C*(α)), 58.0 (*C*(3)), 80.9 (*C*Me$_3$), 118.4 (N(CH$_2$CH=*C*H$_2$)$_2$), 124.2, 124.5, 125.9, 126.2, 127.3, 127.4, 127.7, 128.5, 128.7, 129.4, 134.1, 134.2, 141.4, 143.8, 151.4 (N(CH$_2$CH=CH$_2$)$_2$, *Ar*, *Ph*), 172.1, 173.5 (*C*(1), *C*(2′)); m/z (ESI$^+$) 605 ([M+Na]$^+$, 100%), 583 ([M+H]$^+$, 95%); HRMS (ESI$^+$) $C_{37}H_{47}N_2O_4^+$ ([M+H]$^+$) requires 583.3530; found 583.3532.

4.14. *tert*-Butyl (2*R*,3*S*,α*R*)-2-cyanomethyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(2″-aminophenyl)propanoate 17

Following *general procedure 3*, **14** (371 mg, 0.67 mmol, >99:1 dr), DMBA (627 mg, 4.02 mmol) and Pd(PPh$_3$)$_4$ (46 mg, 40.4 μmol) were reacted in CH_2Cl_2 (10 mL) to give **17** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et$_2$O/Et$_3$N, 75:25:1→50:50:1) gave **17** as a white foam (169 mg, 54%, >99:1 dr); $[\alpha]_D^{25}$ +21.7 (c 1.8, $CHCl_3$); ν_{max} (ATR) 3443, 3374 (N–H), 2977, 2935 (C–H), 2248 (C≡N), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, J 6.8, C(α)*Me*), 1.48 (9H, s, C*Me*$_3$), 2.14 (1H, dd, J 16.4, 3.3, C(1′)H_A), 2.26 (1H, dd, J 16.4, 11.1, C(1′)H_B), 3.31–3.38 (1H, m, C(2)*H*), 3.63 (1H, d, J 14.9, NCH_AH$_B$Ph), 4.03–4.24 (4H, m, C(α)*H*, NCH$_A$$H_BPh, NH_2$), 4.40 (1H, d, J 6.8, C(3)*H*), 6.65 (1H, d, J 7.8, *Ar*), 6.76 (1H, app t, J 7.5, *Ar*), 7.08–7.46 (12H, *Ar*, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.3 (C(α)*Me*), 17.0 (*C*(1′)), 27.9 (C*Me*$_3$), 47.2 (*C*(2)), 51.6 (NCH$_2$Ph), 57.0 (*C*(α)), 62.0 (*C*(3)), 82.8 (*C*Me$_3$), 117.1, 118.4 (*Ar*), 118.4 (*C*(2′)), 121.8, 127.1, 127.2, 128.2, 128.3, 128.4, 128.6, 128.9, 129.8, 140.7, 143.5, 145.6 (*Ar*, *Ph*), 171.0 (*C*(1)); m/z (ESI$^+$) 961 ([2M+Na]$^+$, 53%), 492 ([M+Na]$^+$, 30%), 470 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{35}N_3NaO_2^+$ ([M+Na]$^+$) requires 492.2621; found 492.2622.

4.15. *tert*-Butyl (2*R*,3*S*,α*R*)-2-(2′-*tert*-butoxy-2′-oxoethyl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(2″-aminophenyl) propanoate 18

Following *general procedure 3*, **15** (1.59 g, 2.54 mmol, >99:1 dr), DMBA (1.23 g, 7.87 mmol) and Pd(PPh$_3$)$_4$ (147 mg, 0.13 mmol) were reacted in CH_2Cl_2 (50 mL) to give **18** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et$_2$O, 5:1) gave **18** as a yellow oil (1.02 g, 74%, >99:1 dr); $[\alpha]_D^{25}$ +11.7 (c 0.9, $CHCl_3$); ν_{max} (ATR) 2977 (C–H), 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 1.24–1.32 (12H, m, C(α)*Me*, C*Me*$_3$), 1.34 (9H, s, C*Me*$_3$), 2.03 (1H, dd, J 17.2, 2.8, C(1′)H_A), 2.31 (1H, dd, J 17.2, 11.6, C(1′)H_B), 3.37–3.47 (1H, m, C(2)*H*), 3.63 (1H, d, J 14.9, NCH_AH$_B$Ph), 4.02–4.18 (2H, br s, NH_2), 4.15–4.23 (2H, m, NCH$_A$$H_B$Ph, C(α)*H*), 4.37 (1H, d, J 6.3, C(3)*H*), 6.62 (1H, d, J 7.8, *Ar*), 6.71 (1H, app t, J 7.5, *Ar*), 7.06 (1H, t, J 7.5, *Ar*), 7.09–7.37 (9H, m, *Ar*, *Ph*), 7.47 (2H, d, J 7.6, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.4 (C(α)*Me*), 27.8, 28.0 (2×C*Me*$_3$), 33.5 (*C*(1′)), 46.4 (*C*(2)), 51.9 (NCH$_2$Ph), 57.0 (*C*(α), *C*(3)), 79.7, 80.9 (2×CMe$_3$), 116.7, 118.0, 126.6, 126.9, 128.1, 128.1, 128.1, 128.2, 128.5, 130.1, 141.5, 141.5, 144.1, 145.5 (*Ar*, *Ph*), 171.1, 171.4 (*C*(1), *C*(2′)); m/z (ESI$^+$) 567 ([M+Na]$^+$, 100%), 545 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{34}H_{44}N_2NaO_4^+$ ([M+Na]$^+$) requires 567.3193; found 567.3187.

4.16. *tert*-Butyl (2*R*,3*S*,α*R*)-2-(2′-methoxy-2′-oxoethyl-)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(2″-aminophenyl)propanoate 19

Following general procedure 3, **16** (528 mg, 0.91 mmol, >99:1 dr), DMBA (848 mg, 5.43 mmol) and Pd(PPh$_3$)$_4$ (31 mg, 27.0 μmol) were reacted in CH_2Cl_2 (10 mL) to give **19** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et$_2$O/Et$_3$N, 66:34:1) gave **19** as a white solid (310 mg, 68%, >99:1 dr); mp 147–150 °C; $[\alpha]_D^{25}$ +11.7 (c 1.3, $CHCl_3$); ν_{max} (ATR) 3061, 3027 (N–H), 2975, 2949 (C–H), 1736 (C=O); δ_H (400 MHz, $CDCl_3$) 1.30 (3H, d, J 6.8, C(α)*Me*), 1.36 (9H, s, C*Me*$_3$), 2.18 (1H, dd, J 17.1, 2.7, C(1′)H_A), 2.40 (1H, dd, J 17.1, 11.2, C(1′)H_B), 3.41–3.50 (1H, m, C(2)*H*), 3.42 (3H, s, O*Me*), 3.65 (1H, d, J 14.9, NCH_AH$_B$Ph), 4.02–4.23 (2H, br s, NH_2), 4.14–4.25 (2H, m, C(α)*H*, NCH$_A$$H_B$Ph), 4.40 (1H, d, J 6.3, C(3)*H*), 6.62 (1H, d, J 8.1, *Ar*), 6.71 (1H, app t, J 7.3, *Ar*), 7.06 (1H, app t, J 7.3, *Ar*), 7.11–7.49 (11H, m, *Ar*, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.5 (C(α)*Me*), 27.8 (C*Me*$_3$), 32.5 (*C*(1′)), 46.4 (*C*(2)), 51.2 (O*Me*), 51.9 (NCH_2Ph), 57.0 (*C*(α)), 60.3 (*C*(3)), 81.2 (*C*Me$_3$), 116.8, 118.0, 123.1, 126.5, 126.9, 128.1, 128.1, 128.3, 128.3, 128.5, 129.9, 141.4, 144.0, 145.5 (*Ar*, *Ph*), 172.4, 172.8 (*C*(1), *C*(2′)); m/z (ESI$^+$) 525 ([M+Na]$^+$, 100%), 503 ([M+H]$^+$,

100%); HRMS (ESI$^+$) $C_{31}H_{38}N_2NaO_4^+$ ([M+Na]$^+$) requires 525.2724; found 525.2723.

4.17. (3*R*,4*S*,α*R*)-3-(Cyanomethyl)-4-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3,4-dihydro-1*H*-quinolin-2-one 20

Following *general procedure 4*, **17** (580 mg, 1.23 mmol, >99:1 dr) and $PhCO_2H$ (452 mg, 3.70 mmol) in THF (7.5 mL) was heated at 50 °C for 72 h. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O/Et_3N, 50:50:1→25:75:1) gave **20** as a white solid (488 mg, quant, >99:1 dr); mp 158–163 °C; $[\alpha]_D^{25}$ −28.4 (*c* 2.5, $CHCl_3$); ν_{max} (ATR) 3061, 3027, 2977, 2933 (C–H), 2247 (C≡N), 1680 (C=O); δ_H (400 MHz, $CDCl_3$) 0.99 (3H, d, *J* 6.8, C(α)*Me*), 2.35 (1H, dd, *J* 16.9, 6.8, C(1′)H_A), 2.68–2.97 (1H, m, C(3)*H*), 3.14 (1H, dd, *J* 16.9, 6.8, C(1′)H_B), 3.64 (1H, d, *J* 14.0, NCH_AH$_B$Ph), 3.71 (1H, d, *J* 14.0, NCH$_A$$H_B$Ph), 4.05 (1H, q, *J* 6.8, C(α)*H*), 4.20 (1H, d, *J* 6.6, C(4)*H*), 6.99 (1H, d, *J* 7.8, *Ar*), 7.10–7.43 (13H, m, *Ar*, *Ph*), 9.65 (1H, s, N*H*); δ_C (100 MHz, $CDCl_3$) 14.2 (*C*(1′)), 14.8 (C(α)*Me*), 43.0 (*C*(3)), 50.2 (NCH_2Ph), 55.6 (*C*(4)), 56.9 (*C*(α)), 116.8 (*Ar*), 119.5, 122.7, 123.5, 127.3, 127.5, 127.7, 128.6, 128.6, 129.2, 129.4, 129.5, 137.2, 139.2, 143.5 (*C*(2′), *Ar*, *Ph*), 170.2 (*C*(2)); *m*/*z* (ESI$^+$) 813 ([2M+Na]$^+$, 84%), 418 ([M+Na]$^+$, 49%), 396 ([M+H]$^+$, 10%); HRMS (ESI$^+$) $C_{26}H_{25}N_3NaO^+$ ([M+Na]$^+$) requires 418.1890; found 418.1887.

4.18. (3*R*,4*S*,α*R*)-3-(2′-Oxoethyl)-4-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3,4-dihydro-1*H*-quinolin-2-one 21

DIBAL-H (1.0 M in CH_2Cl_2, 0.62 mL, 0.62 mmol) was added to a stirred solution of **20** (81.4 mg, 0.21 mmol, >99:1 dr) in CH_2Cl_2 (2.0 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 2 h. Satd aq Rochelle's salt (5 mL) was added and the resultant mixture was stirred vigorously at rt for 5 min. The aqueous layer was extracted with EtOAc (2×5 mL) and the combined organic extracts were dried and concentrated in vacuo. The residue was passed through a short plug of silica (eluent 30–40 °C petrol/EtOAc/Et_3N, 50:50:1) to give **21** as a yellow oil (63 mg, 76%, >99:1 dr); $[\alpha]_D^{25}$ −78.3 (*c* 1.0, $CHCl_3$); ν_{max} (ATR) 3061 (C–H), 1721 [C=O (aldehyde)], 1673 [C=O (lactam)]; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, d, *J* 6.8, C(α)*Me*), 2.59–2.69 (1H, m, C(1′)H_A), 3.26–3.37 (2H, m, C(1′)H_B, C(3)*H*), 3.59 (1H, d, *J* 13.8, NCH_AH$_B$Ph), 3.73 (1H, d, *J* 13.8, NCH$_A$$H_B$Ph), 4.00–4.08 (2H, m, C(4)*H*, C(α)*H*), 6.93 (1H, d, *J* 8.1, *Ar*), 7.00–7.17 (3H, m, *Ar*), 7.18–7.40 (10H, m, *Ph*), 9.48 (1H, s, C(2′)*H*), 9.52 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 14.0 (C(α)*Me*), 39.5 (*C*(1′)), 39.6 (*C*(3)), 50.3 (NCH_2Ph), 55.5, 56.1 (*C*(α), *C*(4)), 116.5, 123.1, 123.7, 126.9, 127.2, 127.9, 128.3, 128.4, 129.0, 129.3, 129.5, 137.5, 139.6, 144.0 (*Ar*, *Ph*), 172.4 (*C*(2)), 200.2 (*C*(2′)); *m*/*z* (ESI$^+$) 819 ([2M+Na]$^+$, 100%), 421 ([M+Na]$^+$, 40%), 399 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{26}N_2NaO_2^+$ ([M+Na]$^+$) requires 421.1886; found 421.1883.

4.19. *tert*-Butyl (2*R*,3*S*)-2-(2′-*tert*-butoxy-2′-oxoethyl)-3-amino-3-(2″-aminophenyl)propanoate 23

Pd(OH)$_2$/C (100 mg) was added to a solution of **18** (200 mg, 0.36 mmol, >99:1 dr) in MeOH (15 mL) and the resultant mixture was vigorously stirred under H_2 (4 atm) for 16 h. The resultant suspension was passed through a pad of Celite® (eluent MeOH/Et_3N, 100 mL) and the filtrate was concentrated in vacuo to give **23** as a colourless oil (120 mg, quant, >99:1 dr); $[\alpha]_D^{25}$ +1.2 (*c* 1.0, $CHCl_3$); ν_{max} (ATR) 3429, 3383, 3311 (N–H), 2978, 2932 (C–H), 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 1.39 (9H, s, CMe_3), 1.48 (9H, s, CMe_3), 1.69–1.87 (2H, br s, NH_2), 2.25 (1H, dd, *J* 16.9, 5.3, C(1′)H_A), 2.31 (1H, dd, *J* 16.9, 8.2, C(1′)H_B), 3.27–3.35 (1H, m, C(2)*H*), 4.23 (1H, d, *J* 9.4, C(3)*H*), 4.76–4.86 (2H, m, NH_2), 4.76–4.86 (2H, m, *Ar*), 6.95–7.00 (1H, m, *Ar*), 7.04–7.09 (1H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 28.0, 28.1 (2×CMe_3), 35.9 (*C*(1′)), 45.4 (*C*(2)), 57.4 (*C*(3)), 80.1, 80.5 (2×CMe_3), 116.7, 117.5, 125.2, 128.5, 129.7, 146.3 (*Ar*), 171.1, 173.7 (*C*(1), *C*(2′)); *m*/*z* (ESI$^+$) 351 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{31}N_2O_4^+$ ([M+H]$^+$) requires 351.2278; found 351.2277.

4.20. (3*R*,4*S*)-3-(2′-*tert*-Butoxy-2′-oxoethyl)-4-amino-3,4-dihydro-1*H*-quinolin-2-one 24

Attempted purification of a portion of **23** (231 mg, 0.66 mmol, >99:1 dr) on silica (eluent EtOAc/Et_3N, 100:1) gave **24** as a white solid (74 mg, 40%, >99:1 dr); mp 144–146 °C; $[\alpha]_D^{25}$ −16.0 (*c* 1.0, $CHCl_3$); ν_{max} (ATR) 3029 (N–H), 2778, 2929 (C–H), 1725 [C=O (ester)], 1680 [C=O (δ lactam)]; δ_H (400 MHz, $CDCl_3$) 1.31 (2H, br s, NH_2), 1.49 (9H, s, CMe_3), 2.55 (1H, dd, *J* 16.4, 7.7, C(1′)H_A), 3.06 (1H, dd, *J* 16.4, 6.5, C(1′)H_B), 3.19–3.26 (1H, m, C(3)*H*), 4.09 (1H, d, *J* 4.1, C(4)*H*), 6.86 (1H, d, *J* 7.9, *Ar*), 7.02 (1H, app t, *J* 7.5, *Ar*), 7.19–7.25 (2H, m, *Ar*), 9.22 (1H, d, N(1)*H*); δ_C (100 MHz, $CDCl_3$) 28.1 (CMe_3), 32.0 (C(1′)), 43.2 (*C*(3)), 51.3 (*C*(4)), 80.8 (*C*Me$_3$), 116.0, 123.4, 126.7, 128.1, 128.7, 136.1 (*Ar*), 171.4, 171.7 (*C*(2), *C*(2′)); *m*/*z* (ESI$^+$) 575 ([2M+Na]$^+$, 100%), 299 ([M+Na]$^+$, 62%), 277 ([M+H]$^+$, 84%); HRMS (ESI$^+$) $C_{15}H_{20}N_2NaO_3^+$ ([M+Na]$^+$) requires 299.1366; found 299.1366.

4.21. 3-(2′-Methoxy-2′-oxoethyl)-1*H*-quinolin-2-one 25

A solution of **24** (84 mg, 0.30 mmol, >99:1 dr) in MeOH (4 mL) and HCl (2.0 M in Et_2O, 4 mL) was heated at reflux for 1 h. The reaction mixture was then allowed to cool to rt and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (5 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (5 mL), then dried and concentrated in vacuo to give **25** as a white solid (56 mg, 84%); mp 176–178 °C; ν_{max} (ATR) 2952, 2857 (C–H), 1736 [C=O (ester)], 1665 [C=O (quinolinone)]; δ_H (400 MHz, $CDCl_3$) 3.73 (2H, s, *C*(1′)H_2), 3.75 (3H, s, O*Me*), 7.17–7.22 (1H, m, *Ar*), 7.38–7.57 (3H, m, *Ar*), 7.78 (1H, s, *Ar*), 12.52 (1H, br s, N(1)*H*); δ_C (100 MHz, $CDCl_3$) 35.7 (*C*(1′)), 52.2 (O*Me*), 116.0, 119.9, 122.6, 126.5, 127.5, 130.2, 138.1, 139.4 (*Ar*), 163.9 (*C*(2)), 171.5 (*C*(2′)); *m*/*z* (ESI$^+$) 457 ([2M+Na]$^+$, 100%), 240 ([M+Na]$^+$, 75%); HRMS (ESI$^+$) $C_{12}H_{11}NNaO_3^+$ ([M+Na]$^+$) requires 240.0631; found 240.0630.

4.22. *tert*-Butyl (4*R*,5*S*,α*R*)-2-oxo-5-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-4-carboxylate 26

$PhCO_2H$ (2 mg, 18.0 μmol) was added to a solution of **19** (90.4 mg, 0.18 mmol, >99:1 dr) in PhMe (2 mL) and the resultant solution was heated at reflux for 16 h. The reaction mixture was then allowed to cool to rt and diluted with Et_2O (10 mL). The resultant mixture was washed with satd aq K_2CO_3 (2×5 mL) and the aqueous layer was extracted with Et_2O (5 mL). The combined organic extracts were then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc/Et_3N, 50:50:1) gave **26** as a colourless oil (68 mg, 80%, >99:1 dr); mp 129–132 °C; $[\alpha]_D^{25}$ −1.50 (*c* 1.1, $CHCl_3$); ν_{max} (ATR) 3207 (N–H), 3028, 2976, 2932 (C–H), 1729 [C=O (ester)], 1677 [C=O (lactam)]; δ_H (400 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6.8, C(α)*Me*), 1.39 (9H, s, CMe_3), 2.48 (1H, dd, *J* 14.4, 5.6, C(3)H_A), 2.71 (1H, dd, *J* 14.4, 8.1, C(3)H_B), 3.28–3.35 (1H, m, C(4)*H*), 3.68 (1H, d, *J* 15.2, NCH_AH$_B$Ph), 3.78 (1H, d, *J* 15.2, NCH$_A$$H_B$Ph), 4.12 (1H, q, *J* 6.8, C(α)*H*), 4.56 (1H, d, *J* 5.8, C(5)*H*), 6.86 (1H, d, *J* 7.6, *Ar*), 7.09–7.32 (11H, m, *Ar*, *Ph*), 7.41–7.47 (2H, m, *Ar*), 8.14 (1H, s, N(1)*H*); δ_C (100 MHz, $CDCl_3$) 14.9 (C(α)*Me*), 27.9 (CMe_3), 34.6 (*C*(3)), 48.4 (*C*(4)), 52.7 (NCH_2Ph), 57.5 (*C*(α)), 66.1 (*C*(5)), 81.3 (*C*Me$_3$), 121.9, 124.5, 126.5, 126.9, 128.0, 128.0, 128.0, 128.2, 128.8, 130.9, 132.2, 137.4, 141.1, 143.2 (*Ar*, *Ph*), 171.9, 173.2 (*C*(2), $CO_{2^tBu)}$; *m*/*z* (ESI$^+$) 963 ([2M+Na]$^+$, 40%), 493 ([M+Na]$^+$, 25%), 471 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{34}N_2NaO_3^+$ ([M+Na]$^+$) requires 493.2462; found 493.2465.

4.23. *tert*-Butyl (3*S*,α*R*)-3-[*N*-allyl-*N*-(α-methylbenzyl) amino]-3-(2′-*N*,*N*-diallylaminophenyl)propanoate 29

Following *general procedure 1*, BuLi (2.1 M in hexanes), (*R*)-*N*-allyl-*N*-(α-methylbenzyl)amine[23] (1.20 g, 7.42 mmol, >99:1 er) and **12** (1.39 g, 4.64 mmol, >99:1 dr) were reacted in THF (50 mL) to give **29** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave **29** as a yellow oil (1.80 g, 85%, >99:1 dr); $[\alpha]_D^{25}$ +8.71 (*c* 2.1, $CHCl_3$); ν_{max} (ATR) 3073, 3025, 3004, 2877, 2931, 2816, 2349 (C–H), 1728 (C=O), 1640, 1596 (C=C); δ_H (400 MHz, $CDCl_3$) 1.23 (3H, d, *J* 6.8, C(α)*Me*), 1.36 (9H, s, CMe_3), 2.57 (1H, dd, *J* 15.3, 6.2, C(2)H_A), 2.92 (1H, dd, *J* 15.3, 8.5, C(2)H_B), 3.20 (1H, dd, *J* 15.7, 4.7, NCH_AH_BCH=CH_2), 3.39 (1H, dd, *J* 15.7, 6.7, NCH_AH_BCH=CH_2), 3.49–3.76 (4H, m, N(CH_2CH=CH_2)$_2$), 3.98 (1H, q, *J* 6.8, C(α)*H*), 4.90–5.26 (7H, m, C(3)*H*, NCH_2CH=CH_2, N(CH_2CH=CH_2)$_2$), 5.73–5.96 (3H, m, NCH_2C*H*=CH_2, N(CH_2C*H*=CH_2)$_2$), 7.07–7.31 (6H, m, *Ar*, *Ph*), 7.38 (2H, d, *J* 7.6, *Ph*), 7.55 (1H, d, *J* 7.6, *Ar*); δ_C (100 MHz, $CDCl_3$) 15.7 (C(α)*Me*), 28.0 (CMe_3), 40.4 (*C*(2)), 49.2 (NCH_2CH=CH_2), 53.6 (*C*(3)), 56.3 (*C*(α)), 57.0 (N(CH_2CH=CH_2)$_2$), 80.1 (*C*Me$_3$), 114.5, 117.7 (NCH_2CH=CH_2, N(CH_2CH=CH_2)$_2$), 123.7, 124.1, 126.3, 127.1, 127.8, 127.8, 128.9, 135.0, 139.2, 140.0, 145.2, 150.0 (NCH_2CH=CH_2, N(CH_2C*H*=CH_2)$_2$, *Ar*, *Ph*), 171.6 (*C*(1)); *m*/*z* (ESI$^+$) 483 ([M+Na]$^+$, 98%), 461 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{41}N_2O_2^+$ ([M+H]$^+$) requires 461.3163; found 461.3163.

4.24. *tert*-Butyl (2*R*,3*S*,α*R*)-2-(2′-methoxy-2′-oxoethyl)-3-[*N*-allyl-*N*-(α-methylbenzyl)amino]-3-(2″-*N*,*N*-diallylaminophenyl)propanoate 30

Following *general procedure 2*, ^{i}Pr$_2$NH (11.5 mL, 82.0 mmol), BuLi (2.5 M in hexanes, 31.7 mL, 79.3 mmol), **29** (25.2 g, 54.7 mmol, >99:1 dr) and methyl bromoacetate (15.5 mL, 164 mmol) were reacted in THF (500 mL) to give **30** in >95:5 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O/Et_3N, 86:14:1) gave **30** as a yellow oil (20.0 g, 68%, >99:1 dr); $[\alpha]_D^{20}$ +5.76 (*c* 1.2, $CHCl_3$); ν_{max} (ATR) 3073, 2978, 2820 (C–H), 1742 (C=O); δ_H (400 MHz, $CDCl_3$) 1.04 (3H, app dd, *J* 6.6, 1.3, C(α)*Me*), 1.50 (9H, s, CMe_3), 2.20 (1H, dd, *J* 15.7, 3.0, C(1′)H_A), 2.50 (1H, dd, *J* 15.7, 11.5, C(1′)H_B), 3.10–3.19 (1H, m, NCH_AH_BCH=CH_2), 3.21–3.30 (1H, m, NCH_AH_BCH=CH_2), 3.45–3.67 (8H, m, C(2)*H*, CO_2*Me*, N(CH_2CH=CH_2)$_2$), 4.16 (1H, q, *J* 6.6, C(α)*H*), 4.77–4.89 (2H, m, NCH_2CH=CH_2), 5.03 (1H, d, *J* 11.6, C(3)*H*), 5.12–5.22 (4H, m, N(CH_2CH=CH_2)$_2$), 5.61–5.73 (1H, m, NCH_2C*H*=CH_2), 5.81–5.94 (2H, m, N(CH_2C*H*=CH_2)$_2$), 7.10–7.31 (8H, m, *Ar*, *Ph*), 7.35–7.40 (1H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 18.7 (C(α)*Me*), 28.0 (CMe_3), 35.9 (*C*(1′)), 46.6 (O*Me*), 49.9 (NCH_2CH=CH_2), 51.6 (*C*(2)), 56.5 (*C*(α)), 57.3 (*C*(3)), 57.4 (N(CH_2CH=CH_2)$_2$), 80.7 (*C*Me$_3$), 114.8 (NCH_2CH=CH_2), 118.4 (N(CH_2CH=CH_2)$_2$), 124.4, 124.5, 126.0, 127.6, 127.7, 127.9, 129.1, 134.3, 134.6, 138.7, 145.4, 151.4 (NCH_2CH=CH_2, N(CH_2C*H*=CH_2)$_2$, *Ar*, *Ph*), 172.1, 173.7 (*C*(1), *C*(2′)); *m*/*z* (ESI$^+$) 555 ([M+Na]$^+$, 35%), 533 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{33}H_{45}N_2O_4^+$ ([M+H]$^+$) requires 533.3374; found 533.3377.

4.25. *tert*-Butyl (2*R*,3*S*,α*R*)-2-(2′-methoxy-2′-oxoethyl)-3-[*N*-(α-methylbenzyl)amino]-3-(2″-aminophenyl)propanoate 31

Following *general procedure 3*, **30** (1.07 g, 2.02 mmol, >99:1 dr), DMBA (1.42 g, 9.09 mmol) and Pd(PPh$_3$)$_4$ (350 mg, 0.30 mmol) were reacted in CH_2Cl_2 (20 mL) to give **31** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O/Et_3N, 66:34:1) gave **31** as a yellow oil (631 mg, 76%, >99:1 dr); $[\alpha]_D^{20}$ −1.6 (*c* 1.15, $CHCl_3$); ν_{max} (ATR) 3428, 3298 (N–H), 3027, 2974, 2930 (C–H), 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 1.38 (3H, d, *J* 6.6, C(α)*Me*), 1.50 (9H, s, CMe_3), 2.21 (1H, dd, *J* 16.9, 4.6, C(1′)H_A), 2.45 (1H, dd, *J* 16.9, 9.8, C(1′)H_B), 3.43 (1H, app td, *J* 9.8, 4.6, C(2)*H*), 3.58 (3H, s, O*Me*), 3.62 (1H, q, *J* 6.6, C(α)*H*), 4.08 (1H, d, *J* 9.6, C(3)*H*), 4.76 (2H, br s, NH_2), 6.51 (1H, d, *J* 7.8, *Ar*), 6.62 (1H, app t, *J* 7.3, *Ar*), 6.92 (1H, d, *J* 6.8, *Ar*), 7.03 (1H, app td, *J* 7.6, 1.5, *Ar*), 7.15–7.29 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.0 (C(α)*Me*), 28.1 (CMe_3), 34.7 (*C*(1′)), 44.5 (*C*(2)), 51.5 (O*Me*), 54.5 (*C*(α)), 62.7 (*C*(3)), 81.4 (*C*Me$_3$), 116.5, 117.4, 122.4, 126.3, 126.6, 128.2, 128.5, 130.8, 145.8, 146.6 (*Ar*, *Ph*), 172.3, 173.6 (*C*(1), *C*(2′)); *m*/*z* (ESI$^+$) 413 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{33}N_2O_4^+$ ([M+H]$^+$) requires 413.2435; found 413.2443.

4.26. (3a*R*,9b*S*,α*R*)-*N*(1)-(α-Methylbenzyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-2,4-dione 32

Following *general procedure 4*, **31** (280 mg, 0.68 mmol, >99:1 dr) and $PhCO_2H$ (9 mg, 68 μmol) were reacted in PhMe (5 mL) at reflux for 16 h to give **32**. Purification via flash column chromatography (eluent EtOAc/Et_3N, 100:1) gave **32** as a white solid (166 mg, 80%, >99:1 dr); mp 174–177 °C; $[\alpha]_D^{20}$ +86.8 (*c* 0.7, $CHCl_3$); ν_{max} (ATR) 3216 (N–H), 3061, 2988, 2924 (C–H), 1682 [C=O (γ-lactam)], 1616 [C=O (δ-lactam)]; δ_H (400 MHz, $CDCl_3$) 1.04 (3H, d, *J* 7.1, C(α)*Me*), 2.81 (1H, dd, *J* 16.7, 8.1, C(3)H_A), 3.06–3.14 (1H, m, C(3a)*H*), 3.31 (1H, d, *J* 16.7, C(3)H_B), 4.72 (1H, d, *J* 5.6, C(9b)*H*), 5.49 (1H, q, *J* 7.1, C(α)*H*), 6.29 (1H, d, *J* 7.3, *Ar*), 6.85 (1H, app t, *J* 7.4, *Ar*), 6.93 (2H, d, *J* 7.8, *Ph*), 7.26–7.40 (5H, m, *Ar*, *Ph*), 10.04 (1H, br s, N(5)*H*); δ_C (100 MHz, $CDCl_3$) 16.7 (C(α)*Me*), 34.3 (*C*(3)), 38.6 (*C*(3a)), 49.1 (*C*(α)), 57.7 (*C*(9b)), 116.0, 117.3, 122.7, 127.3, 127.5, 128.5, 130.7, 131.6, 137.3, 139.0 (*Ar*, *Ph*), 171.0, 173.6 (*C*(2), *C*(4)); *m*/*z* (ESI$^+$) 635 ([2M+Na]$^+$, 100%), 613 ([2M+H]$^+$, 30%), 329 ([M+Na]$^+$, 55%); HRMS (ESI$^+$) $C_{19}H_{18}N_2NaO_2^+$ ([M+Na]$^+$) requires 329.1260; found 329.1261.

4.27. (3a*R*,9b*S*,α*R*)-*N*(1)-(α-Methylbenzyl)-*N*(5)-(*tert*-butoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinolin-2,4-dione 33

Boc_2O (6.68 g, 30.6 mmol), Et_3N (6.40 mL, 45.9 mmol) and DMAP (93 mg, 0.78 mmol) were added sequentially to a stirred solution of **32** (4.69 g, 15.3 mmol, >99:1 dr) in CH_2Cl_2 (150 mL) and the resultant mixture was stirred at 35 °C for 16 h. The reaction mixture was then washed with 1.0 M aq HCl (100 mL) and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (50 mL) and brine (50 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc/Et_3N, 50:50:1→0:100:1) gave **33** as a yellow solid (5.14 g, 83%, >99:1 dr); $C_{24}H_{26}N_2O_4$ requires C, 70.9; H, 6.45; N, 6.9%; found C, 70.8; H, 6.6; N, 7.0%; mp 155–168 °C; $[\alpha]_D^{20}$ +53.3 (*c* 2.1, $CHCl_3$); ν_{max} (ATR) 2981, 2936 (C–H), 1766, 1694 [C=O (δ lactam)], 1608 [C=O (carbamate)]; δ_H (400 MHz, $CDCl_3$) 1.06 (3H, d, *J* 7.3, C(α)*Me*), 1.61 (9H, s, CMe_3), 2.73 (1H, dd, *J* 16.4, 7.5, C(3)H_A), 3.08–3.14 (1H, m, C(3a)*H*), 3.28 (1H, d, *J* 16.4, C(3)H_B), 4.63 (1H, d, *J* 5.3, C(9b)*H*), 5.48 (1H, q, *J* 7.3, C(α)*H*), 6.26 (1H, d, *J* 7.6, *Ar*), 6.87–6.95 (1H, m, *Ar*), 7.04–7.10 (2H, d, *J* 7.8, *Ph*), 7.28–7.39 (5H, m, *Ar*, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.7 (C(α)*Me*), 27.6 (CMe_3), 34.5 (*C*(3)), 39.5 (*C*(3a)), 48.9 (*C*(α)), 57.4 (*C*(9b)), 85.8 (*C*Me$_3$), 116.1, 118.6, 123.7, 127.4, 127.4, 128.5, 130.6, 131.9, 137.1, 138.9 (*Ar*, *Ph*), 150.8 (NCO), 167.7, 173.2 (*C*(2), *C*(4)); *m*/*z* (ESI$^+$) 429 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{26}N_2NaO_4^+$ ([M+Na]$^+$) requires 429.1785; found 429.1782.

4.28. (3a*R*,4*R*,9b*S*,α*R*)- or (3a*R*,4*S*,9b*S*,α*R*)-*N*(1)-(α-Methylbenzyl)-4-hydroxy-*N*(5)-(*tert*-butoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinolin-2-one 34

$LiAl(O^tBu)_3H$ (5.44 g, 21.4 mmol) was added to a stirred solution of **33** (4.35 g, 10.7 mmol, >99:1 dr) in THF (100 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 1 h. H_2O (1 mL) was then added dropwise, EtOAc (20 mL) was added, and the resultant mixture was allowed to stir at rt for 10 min. The reaction mixture was then filtered through a pad of Celite® (eluent EtOAc), then

dried and concentrated in vacuo to give **34** as a white foam (4.40 g, quant, >99:1 dr). An aliquot was purified via flash column chromatography (eluent EtOAc/Et_3N, 100:1) to give an analytically pure sample of **34** as a white foam (>99:1 dr);[46] $[\alpha]_D^{20}$ +68.6 (*c* 1.6, $CHCl_3$); ν_{max} (ATR) 3429 (O–H), 3032, 2951 (C–H), 1695 [C=O (carbamate)], 1664 [C=O (γ lactam)]; δ_H (400 MHz, $CDCl_3$) 0.94 (3H, d, *J* 7.3, C(α)*Me*), 1.47 (9H, s, C*Me*$_3$), 2.54 (1H, dd, *J* 16.8, 1.9, C(3)H_A), 2.76–2.92 (2H, m, C(3)H_B, C(3a)*H*), 3.74 (1H, br s, O*H*), 4.48 (1H, d, *J* 7.3, C(9b)*H*), 5.38 (1H, s, C(4)*H*), 5.47 (1H, q, *J* 7.3, C(α)*H*), 6.38 (1H, dd, *J* 7.6, 1.0, *Ar*), 6.93 (1H, td, *J* 7.5, 1.3, *Ar*), 7.05 (2H, d, *J* 7.8, *Ph*), 7.24–7.38 (5H, m, *Ar*, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.5 (C(α)*Me*), 28.3 (C*Me*$_3$), 36.1 (*C*(3)), 42.2 (*C*(3a)), 49.8 (*C*(α)), 56.9 (*C*(9b)), 81.9, 81.9 (*C*(4), C*Me*$_3$), 124.3, 126.0, 127.3, 127.8, 128.2, 129.1, 130.4, 137.4, 138.6 (*Ar*, *Ph*), 152.7 (NCO), 173.5 (*C*(2)); *m*/*z* (ESI$^+$) 839 ([2M+Na]$^+$, 100%), 431 ([M+Na]$^+$, 76%); HRMS (ESI$^+$) $C_{24}H_{28}N_2NaO_4^+$ ([M+Na]$^+$) requires 431.1941; found 431.1937.

4.29. (3a*S*,4*S*,9b*S*,α*R*)-*N*(1)-(α-Methylbenzyl)-4-[2′-methoxy-2′-oxoethyl]-*N*(5)-(*tert*-butoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinolin-2-one 35

Phosphorane **38** (7.15 g, 21.4 mmol) was added to a solution of **34** (4.40 g, 10.7 mmol) in PhMe (100 mL) and the resultant mixture was stirred at 80 °C for 72 h. The reaction mixture was then concentrated in vacuo to give **35** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc/Et_3N, 75:25:1) followed by trituration with Et_2O to gave **35** as a yellow oil (3.97 g, 80%, >99:1 dr); $[\alpha]_D^{20}$ +96.8 (*c* 0.7, $CHCl_3$); ν_{max} (ATR) 2976, 2934 (C–H), 1739 [C=O (ester)], 1695 [C=O (carbamate, lactam)]; δ_H (400 MHz, $CDCl_3$) 0.91 (3H, d, *J* 7.1, C(α)*Me*), 1.50 (9H, s, C*Me*$_3$), 2.04–2.17 (2H, m, C(1′)H_2), 2.65–2.78 (2H, m, C(3)H_A, C(3a)*H*), 2.85–2.99 (4H, m, C(3)H_B, O*Me*), 4.44 (1H, d, *J* 7.8, C(9b)*H*), 4.80–4.93 (1H, br m, C(4)*H*), 5.46 (1H, q, *J* 7.1, C(α)*H*), 6.38 (1H, d, *J* 7.3, *Ar*), 6.92–6.99 (1H, m, *Ar*), 7.07 (2H, d, *J* 7.8, *Ph*), 7.25–7.40 (5H, m, *Ar*, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.6 (C(α)*Me*), 28.3 (C*Me*$_3$), 38.4, 39.1 (*C*(3), *C*(1′)), 39.8 (*C*(3a)), 49.7 (*C*(α)), 51.7 (O*Me*), 56.0 (*C*(4)), 56.7 (*C*(9b)), 81.5 (*C*Me$_3$), 124.5, 126.7, 127.3, 127.8, 128.3, 129.0, 129.2, 130.3, 138.6, 138.7 (*Ar*, *Ph*), 152.8 (NCO), 170.8, 173.7 (*C*(2), *C*(2′)); *m*/*z* (ESI$^+$) 951 ([2M+Na]$^+$, 99%), 487 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{32}N_2NaO_5^+$ ([M+Na]$^+$) requires 487.2203; found 487.2199.

4.30. (3a*S*,4*S*,9b*S*,α*R*)-*N*(1)-(α-Methylbenzyl)-4-(2′-methoxy-2′-oxoethyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinolin-2-one 36

TFA (6.0 mL) was added to a stirred solution of **35** (3.97 g, 8.54 mmol, >99:1 dr) in CH_2Cl_2 (60 mL) at rt and the resultant mixture was stirred at 35 °C for 4 h. The reaction mixture was then allowed to cool to rt and neutralised carefully with satd aq K_2CO_3. The resultant solution was washed with satd aq K_2CO_3 (2×50 mL) and the combined aqueous layers were extracted with CH_2Cl_2 (50 mL). The combined organic extracts were then dried and concentrated in vacuo to give **36** as a pale yellow solid. Purification via recrystallisation (CH_2Cl_2/pentane) gave **36** as a white solid (1.61 g, 58%, >99:1 dr); mp 150–155 °C; $[\alpha]_D^{20}$ −31.7 (*c* 1.01, $CHCl_3$); ν_{max} (ATR) 3392, 3338 (N–H), 3029, 2973, 2847 (C–H), 1731 [C=O (ester)], 1678 [C=O (γ lactam)]; δ_H (400 MHz, $CDCl_3$) 1.33 (3H, d, *J* 7.3, C(α)*Me*), 2.17–2.25 (1H, m, C(3a)*H*), 2.32 (1H, dd, *J* 16.7, 1.5, C(1′)H_A), 2.39 (1H, dd, *J* 16.2, 10.1, C(3)H_A), 2.65 (1H, dd, *J* 16.2, 2.5, C(3)H_B), 2.73 (1H, dd, *J* 16.7, 7.0, C(1′)H_B), 3.47 (1H, br t, C(4)*H*), 3.72 (3H, s, O*Me*), 4.63 (1H, app d, *J* 5.1, C(9b)*H*), 4.91 (1H, s, N(5)*H*), 5.38 (1H, q, *J* 7.3, C(α)*H*), 6.40 (1H, dd, *J* 7.8, 1.1, *Ar*), 6.51 (1H, app td, *J* 7.3, 1.0, *Ar*), 6.56 (1H, dd, *J* 8.1, 0.8, *Ar*), 7.08 (1H, app td, *J* 7.6, 1.5, *Ar*), 7.12–7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.6 (C(α)*Me*), 35.9 (*C*(1′)), 36.0 (*C*(3a)), 38.2 (*C*(3)), 48.1 (*C*(4)), 49.3 (*C*(α)), 52.0 (O*Me*), 56.7 (*C*(9b)), 115.0, 115.6, 117.0, 126.9, 127.3, 128.3, 129.9, 132.4, 140.1, 144.3 (*Ar*, *Ph*), 172.5, 173.5 (*C*(2), *C*(2′)); *m*/*z* (ESI$^+$) 751 ([2M+Na]$^+$, 100%), 387 ([M+Na]$^+$, 90%); HRMS (ESI$^+$) $C_{22}H_{24}N_2NaO_3^+$ ([M+Na]$^+$) requires 387.1679; found 387.1665.

4.31. (3a*S*,4*S*,9b*S*,α*R*)-*N*(1)-(α-Methylbenzyl)-4-(2′-hydroxyethyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 37

$LiAlH_4$ (2.0 M in Et_2O, 8.40 mL, 16.8 mmol) was added to a solution of **36** (1.53 g, 4.20 mmol, >99:1 dr) in THF (60 mL) at 0 °C. The resultant mixture was heated at reflux for 16 h, then allowed to cool to rt and subsequently cooled to 0 °C. Aq NaOH (2.0 M, 5.0 mL) was carefully added then the reaction mixture was diluted with EtOAc (20 mL) and the resultant mixture was stirred at rt for 20 min. The reaction mixture was then filtered through a pad of Celite® (eluent EtOAc/Et_3N, 100:1, 150 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 90:10, $CHCl_3$/MeOH) gave **37** as a yellow oil (898 mg, 67%, >99:1 dr); $[\alpha]_D^{20}$ −99.1 (*c* 1.2, $CHCl_3$); ν_{max} (ATR) 3390 (O–H), 3025, 2965, 2934, 2876 (C–H); δ_H (400 MHz, $CDCl_3$) 1.54 (3H, d, *J* 6.6, C(α)*Me*), 1.55–1.73 (2H, m, C(3)H_A, C(1′)H_A), 1.79–1.91 (1H, m, C(1′)H_B), 1.92–2.10 (2H, m, C(3)H_B, C(3a)*H*), 2.58–2.72 (2H, m, C(2)H_2), 3.41 (1H, dt, *J* 8.6, 2.2, C(4)*H*), 3.71 (1H, d, *J* 5.3, C(9b)*H*), 3.73–3.82 (1H, m, C(2′)H_A), 3.85–3.93 (1H, m, C(2′)H_B), 4.34 (1H, q, *J* 6.6, C(α)*H*), 6.62 (1H, d, *J* 7.8, *Ar*), 6.67–6.72 (1H, m, *Ar*), 7.06–7.12 (1H, m, *Ar*), 7.17–7.34 (4H, m, *Ar*, *Ph*), 7.41 (2H, d, *J* 7.3, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.2 (C(α)*Me*), 26.1 (*C*(3)), 35.6 (*C*(1′)), 39.6 (*C*(3a)), 42.9 (*C*(2)), 52.3 (*C*(4)), 53.7 (*C*(α)), 58.7 (*C*(9b)), 61.5 (*C*(2′)), 114.6, 116.6, 120.6, 126.4, 127.5, 127.9, 128.1, 131.1, 144.7, 144.9 (*Ar*, *Ph*); *m*/*z* (ESI$^+$) 323 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{27}N_2O^+$ ([M+H]$^+$) requires 323.2118; found 322.2108.

4.32. (3a*S*,4*S*,9b*S*,α*R*)-*N*(1)-(α-Methylbenzyl)-4-[2′-(4″-toluenesulfonyloxy)ethyl]-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 39 and (3a*S*,4*S*,9b*S*,α*R*)-*N*(1)-(α-methylbenzyl)-4-(2′-chloroethyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*] quinoline 40

Method A: CCl_4 (0.78 mL, 7.80 mmol) was added to a solution of **37** (257 mg, 0.80 mL, >99:1 dr), PPh_3 (523 mg, 2.00 mmol) and Et_3N (1.11 mL, 7.80 mmol) in MeCN (10 mL) at 0 °C. The resultant mixture was stirred at rt for 16 h then was concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 75:25) gave **40** as a yellow oil (196 mg, 72%, >99:1 dr); $[\alpha]_D^{20}$ −64.9 (*c* 1.3, $CHCl_3$); ν_{max} (ATR) 3410 (N–H), 2965, 2931, 2875 (C–H); δ_H (500 MHz, $CDCl_3$); 1.50 (3H, d, *J* 6.6, C(α)*Me*), 1.62–1.72 (1H, m, C(3)H_A), 1.90–2.14 (4H, m, C(3)H_B, C(3a)*H*, C(1′)H_2), 2.59–2.72 (2H, m, C(2)H_2), 3.48 (1H, td, *J* 7.9, 3.2, C(4)*H*), 3.65–3.74 (3H, m, C(9b)*H*, C(2′)H_2), 4.08 (1H, br s, N(5)*H*), 4.20 (1H, q, *J* 6.6, C(α)*H*), 6.57 (1H, d, *J* 7.9, *Ar*), 7.05 (1H, app td, *J* 7.6, 1.3, *Ar*), 7.17–7.22 (3H, m, *Ar*, *Ph*), 7.26–7.31 (2H, m, *Ph*), 7.38 (2H, d, *J* 7.6, *Ph*); δ_C (125 MHz, $CDCl_3$) 12.9 (C(α)*Me*), 26.5 (*C*(3)), 36.6 (*C*(1′)), 39.3 (*C*(3a)), 42.2 (*C*(2′)), 43.6 (*C*(2)), 50.8 (*C*(4)), 54.9 (*C*(α)), 58.3 (*C*(9b)), 114.4, 117.1, 121.3, 126.4, 127.4, 128.0, 128.0, 130.8, 144.0, 145.0 (*Ar*, *Ph*); *m*/*z* 341 ([M(^{35}Cl)+H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{26}{}^{35}ClN_2^+$ ([M(^{35}Cl)+H]$^+$) requires 341.1779; found 341.1778.

Method B: DMAP (11 mg, 91 μmol), Et_3N (0.19 mL, 1.36 mmol) and TsCl (208 mg, 1.09 mmol) were added sequentially to a stirred solution of **37** (293 mg, 0.91 mmol) in CH_2Cl_2 (20 mL) and the resultant mixture was stirred at rt for 16 h. The reaction mixture was washed with 1.0 M aq HCl (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (10 mL) and brine (10 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc/Et_3N, 66:34:1) gave **40** as a yellow oil (72 mg, 23%, >99:1 dr). Further

elution gave **39** as a yellow oil (180 mg, 41%, ~90% purity); $[\alpha]_D^{20}$ −82.2 (*c* 1.2, $CHCl_3$); ν_{max} (ATR) 3401 (N–H), 3055, 3026, 2966, 2931, 2876 (C–H); δ_H (400 MHz, $CDCl_3$) 1.48 (3H, d, *J* 6.6, C(α)*Me*), 1.52–1.64 (1H, m, C(3)H_A), 1.70–1.81 (1H, m, C(1′)H_A), 1.86–2.06 (3H, m, C(3)H_B, C(3a)*H*, C(1′)H_B), 2.45 (3H, s, C(4″)*Me*), 2.52–2.71 (2H, m, C(2)H_2), 3.36 (1H, td, *J* 8.0, 2.8, C(4)*H*), 3.66 (1H, d, *J* 5.3, C(9b)*H*), 4.12–4.29 (3H, m, C(α)*H*, C(2′)H_2), 6.46 (1H, d, *J* 7.3, *Ar*), 6.66 (1H, app td, *J* 7.3, 1.0, *Ar*), 7.03 (1H, app td, *J* 7.6, 1.4, *Ar*), 7.16 (1H, d, *J* 6.6, *Ar*), 7.20 (1H, t, *J* 7.0, *Ph*), 7.28 (2H, app t, *J* 7.0, *Ph*), 7.32–7.40 (4H, m, C(3″)*H*, C(5″)*H*, *Ph*), 7.83 (2H, d, *J* 8.3, C(2″)*H*, C(6″)*H*); δ_C (100 MHz, $CDCl_3$) 12.8 (C(α)*Me*), 21.7 (C(4″)*Me*), 26.3 (*C*(3)), 32.9 (*C*(1′)), 39.3 (*C*(3a)), 43.5 (*C*(2)), 49.9 (*C*(4)), 54.8 (*C*(α)), 58.2 (*C*(9b)), 68.1 (*C*(2′)), 114.4, 117.0, 121.0, 126.4, 127.4, 127.9, 128.0, 130.0, 130.8, 132.9, 143.8, 145.0 (*C*(2″), *C*(3″), *C*(5″), *C*(6″), *Ar*, *Ph*); *m*/*z* (ESI$^+$) 477 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{33}N_2O_3S^+$ ([M+H]$^+$) requires 477.2206; found 477.2206.

4.33. (3a*S*,4*S*,9b*S*,α*R*)-*N*(1)-(α-Methylbenzyl)-4-(2′-chloroethyl)-8-bromo−2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 41 and (3a*S*,4*S*,9b*S*,α*R*)-*N*(1)-(α-methylbenzyl)-4-(2′-chloroethyl)-6,8-dibromo-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 42

A solution of NBS (39.0 mg, 0.22 mmol) in MeCN (0.6 mL) was added to a solution of **40** (71 mg, 0.21 mmol, >99:1 dr) in MeCN (1 mL) at 0 °C over a period of 10 min. The resultant mixture was stirred at rt for 2 h, then diluted with $CHCl_3$ (50 mL) and washed with H_2O (2×10 mL). The combined aqueous layers were extracted with $CHCl_3$ (20 mL) and the combined organic extracts were washed with brine (2×20 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 60:40) gave **42** as a colourless oil (6.2 mg, 6%, ~90% purity); $[\alpha]_D^{20}$ −47.8 (*c* 0.37, $CHCl_3$); ν_{max} (ATR) 3396 (N–H), 2962, 2928 (C–H); δ_H (400 MHz, $CDCl_3$) 1.38 (3H, d, *J* 6.6, C(α)*Me*), 1.54–1.66 (1H, m, C(3)H_A), 1.75–2.06 (4H, m, C(3)H_B, C(3a)*H*, C(1′)H_2), 2.59–2.69 (2H, m, C(2)H_2), 3.43–3.51 (1H, m, C(4)*H*), 3.54–3.65 (3H, m, C(9b)*H*, C(2′)H_2), 3.93 (1H, q, *J* 6.6, C(α)*H*), 4.68 (1H, br s, N(5)*H*), 7.10–7.17 (2H, *Ar*, *Ph*), 7.18–7.29 (4H, m, *Ph*), 7.32 (1H, d, *J* 2.2, *Ar*); δ_C (100 MHz, $CDCl_3$) [selected peaks] 15.1 (C(α)*Me*), 26.8 (*C*(3)), 28.0 (*C*(3a)), 36.6 (*C*(1′)), 42.0 (*C*(2′)), 44.7 (*C*(2)), 56.9 (*C*(α)), 58.6 (*C*(9b)), 126.8, 127.3, 128.2, 132.4, 132.9, 144.6 (*Ar*, *Ph*); *m*/*z* (ESI$^+$) 499 ([M(^{79}Br^{81}Br^{35}Cl)+H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{24}{}^{79}Br^{81}Br^{35}ClN_2{}^+$ ([M(^{79}Br^{81}Br^{35}Cl)+H]$^+$) requires 498.9969; found 498.9957. Further elution gave **41** as a yellow oil (60 mg, 68%, >99:1 dr); $[\alpha]_D^{20}$ −65.2 (*c* 1.55, $CHCl_3$); ν_{max} (ATR) 3416 (N–H), 3058, 3025, 2964, 2932, 2874 (C–H); δ_H (300 MHz, $CDCl_3$) 1.37 (3H, d, *J* 6.7, C(α)*Me*), 1.47–1.64 (1H, m, C(3)H_A), 1.70–2.02 (4H, m, C(3)H_B, C(3a)*H*, C(1′)H_2), 2.52–2.64 (2H, m, C(2)H_2), 3.29–3.40 (1H, m, C(4)*H*), 3.49–3.59 (3H, m, C(9b)*H*, C(2′)H_2), 3.96 (1H, q, *J* 6.7, C(α)*H*), 6.31 (1H, d, *J* 8.5, C(6)*H*), 6.99 (1H, dd, *J* 8.5, 2.3, C(7)*H*), 7.06–7.32 (6H, m, C(9)*H*, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.6 (C(α)*Me*), 26.8 (*C*(3)), 36.6 (*C*(1′)), 39.2 (*C*(3a)), 42.1 (*C*(2′)), 44.5 (*C*(2)), 50.7 (*C*(4)), 56.4 (*C*(α)), 58.2 (*C*(9b)), 108.7, 116.0, 123.8, 126.7, 127.4, 128.2, 130.6, 133.1, 142.8, 144.9 (*Ar*, *Ph*); *m*/*z* (ESI$^+$) 421 ([M(^{81}Br^{35}Cl)+H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{25}{}^{81}Br^{35}ClN_2{}^+$ ([M(^{81}Br^{35}Cl)+H]$^+$) requires 421.0864; found 421.0849.

4.34. (3a*S*,4*S*,9b*S*,α*R*)-*N*(1)-(α-Methylbenzyl)-4-(2′-chloroethyl)-8-(methoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 43

Following *general procedure 6*, $Pd(OAc)_2$ (11.4 mg, 51 μmol), Xantphos (59 mg, 0.10 mmol), **41** (213 mg, 0.51 mmol) and Et_3N (3.4 mL) were reacted in MeOH (0.6 mL) at 70 °C for 16 h. The reaction mixture was resubjected to the reaction conditions once more, then purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 75:25) gave **43** as a colourless oil (35 mg, 17%, >99:1 dr); $[\alpha]_D^{20}$ −73.5 (*c* 1.06, $CHCl_3$); ν_{max} (ATR) 3371 (N–H), 2950, 2876, 2839 (C–H), 1689 (C=O); δ_H (400 MHz, $CDCl_3$) 1.50 (3H, d, *J* 6.8, C(α)*Me*), 1.57–1.68 (1H, m, C(3)H_A), 1.87–2.14 (4H, m, C(3)H_B, C(3a)*H*, C(1′)H_2), 2.61–2.70 (2H, m, C(2)H_2), 3.45–3.58 (1H, m, C(4)*H*), 3.63–3.74 (3H, m, C(2′)H_2, C(9b)*H*), 3.85 (3H, s, O*Me*), 4.13 (1H, q, *J* 6.8, C(α)*H*), 4.64 (1H, s, N(5)*H*), 6.51 (1H, d, *J* 8.2, C(6)*H*), 7.13–7.20 (1H, m, *Ph*), 7.22–7.29 (2H, m, *Ph*), 7.32 (2H, d, *J* 7.5, *Ph*), 7.71 (1H, dd, *J* 8.2, 1.7, C(7)*H*), 7.84 (1H, d, *J* 1.7, C(9)*H*); δ_C (125 MHz, $CDCl_3$) 13.0 (C(α)*Me*), 26.4 (*C*(3)), 36.6 (*C*(1′)), 38.8 (*C*(3a)), 42.1 (*C*(2′)), 43.6 (*C*(2)), 50.8 (*C*(4)), 51.6 (O*Me*), 55.0 (*C*(α)), 58.5 (*C*(9b)), 113.4, 118.0, 119.5, 126.5, 127.4, 128.0, 130.1, 133.4, 144.9, 148.0 (*Ar*, *Ph*), 167.4 (*C*O_2Me); *m*/*z* (ESI$^+$) 399 ([M(^{35}Cl)+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{28}{}^{35}ClN_2O_2{}^+$ ([M(^{35}Cl)+H]$^+$) requires 399.1834; found 399.1820.

4.35. (3a*S*,4*S*,9b*S*,α*R*)-*N*(1)-(α-Methylbenzyl)-4-(2′-cyanoethyl)-8-(methoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 44

NaCN (10 mg, 0.19 mmol) was added to a solution of **43** (50 mg, 0.13 mmol, >99:1 dr) in DMSO (1.0 mL) and the resultant mixture was heated at 90 °C for 16 h. The reaction mixture was allowed to cool to rt and was then partitioned between H_2O (10 mL) and EtOAc (20 mL). The organic layer was washed with H_2O (3×10 mL) and the combined aqueous layers were extracted with EtOAc (3×10 mL). The combined organic extracts were washed with brine (10 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 50:50) gave **44** as a pale brown oil (38 mg, 79%, >99:1 dr); $[\alpha]_D^{20}$ −70.0 (*c* 0.96, $CHCl_3$); ν_{max} (ATR) 3374 (N–H), 2949, 2876, 2849 (C–H), 2247 (C≡N), 1703 (C=O); δ_H (500 MHz, $CDCl_3$) 1.50 (3H, d, *J* 6.6, C(α)*Me*), 1.57–1.66 (1H, m, C(3)H_A), 1.87–2.07 (4H, m, C(3)H_B, C(3a)*H*, C(1′)H_2), 2.44 (1H, dd, *J* 17.0, 7.3, C(2′)H_A), 2.51 (1H, dd, *J* 17.0, 7.6, C(2′)H_B), 2.62–2.72 (2H, m, C(2)H_2), 3.47–3.56 (1H, br m, C(4)*H*), 3.70 (1H, d, *J* 4.1, C(9b)*H*), 3.86 (3H, s, O*Me*), 4.13 (1H, q, *J* 6.6, C(α)*H*), 4.49 (1H, br s, N(5)*H*), 6.54 (1H, d, *J* 8.5, C(6)*H*), 7.13–7.19 (1H, m, *Ph*), 7.21–7.34 (4H, m, *Ph*), 7.72 (1H, d, *J* 8.5, C(7)*H*), 7.84 (1H, s, C(9)*H*); δ_C (125 MHz, $CDCl_3$) 12.9 (C(α)*Me*), 13.2 (*C*(2′)), 26.1 (*C*(3)), 29.3 (*C*(1′)), 37.8 (*C*(3a)), 43.4 (*C*(2)), 51.2 (*C*(4)), 51.7 (O*Me*), 54.8 (*C*(α)), 58.5 (*C*(9b)), 113.7 (*C*(6)), 118.4, 119.5 (*Ar*), 119.7 (*C*(3′)), 126.5, 127.3, 128.0 (*Ph*), 130.2 (*C*(7)), 133.4 (*C*(9)), 144.7, 147.9 (*Ar*, *Ph*), 167.3 (*C*O_2Me); *m*/*z* (ESI$^+$) 412 ([M+Na]$^+$, 25%), 390 ([M+H]$^+$, 100%); HMRS (ESI$^+$) $C_{24}H_{28}N_3O_2{}^+$ ([M+H]$^+$) requires 390.2176; found 390.2164.

4.36. (3a*S*,3b*S*,11b*S*,α*R*)-*N*(1)-(α-Methylbenzyl)-10-(1′-oxo-1′-methoxy)-2,3,3a,3b,4,5,6,11b-octahydro-1*H*-dipyrrolo[1,2-*a*:3′,2′-*c*]quinoline 45

$Pd(OH)_2$/C (5 mg) was added to a stirred, degassed solution of **44** (10 mg, 0.1 mmol, >99:1 dr) in HCl (0.4 M in MeOH, 2 mL). The resultant mixture was purged with H_2 and stirred vigorously under H_2 (1 atm) at rt for 16 h. The mixture was then purged with N_2, filtered through a short pad of Celite® (eluent MeOH/Et_3N, 100:1, 10 mL) and concentrated in vacuo. The residue was dissolved in EtOAc (10 mL) and the resultant solution was washed with 2.0 M aq NaOH (2×10 mL). The organic layer was then dried and concentrated in vacuo. Purification via flash column chromatography (eluent EtOAc/Et_3N, 100:1) gave **45** as a colourless oil (3 mg, 30%, ~90% purity); ν_{max} (ATR) 2360, 2341 (C–H), 1703 (C=O); δ_H (400 MHz, C_6D_6) 1.00–1.14 (1H, m, C(4)H_A), 1.23–1.34 (1H, m, C(5)H_A), 1.36–1.53 (5H, m, C(3)H_A, C(3a)*H*, C(α)*Me*), 1.57–1.65 (1H, m, C(3)H_B), 1.65–1.74 (1H, m, C(5)H_B), 1.77–1.85 (1H, m, C(4)H_B), 2.42–2.51 (1H, m, C(6)H_A), 2.60 (1H, td, *J* 8.9, 4.7, C(6)H_B), 2.87–2.95 (1H, m, C(2)H_A), 3.06 (1H, td, *J* 9.5, 1.6, C(2)H_B), 3.40 (1H, td, *J* 10.4, 5.0, C(3b)*H*), 3.58 (1H, d, *J* 4.4, C(11b)*H*), 3.78 (3H, s, O*Me*), 4.60 (1H,

q, *J* 6.6, C(α)*H*), 6.42 (1H, d, *J* 8.5, C(8)*H*), 7.09–7.15 (1H, m, *Ph*), 7.20 (2H, app t, *J* 7.6, *Ph*), 7.36 (2H, d, *J* 7.6, *Ph*), 8.36 (1H, d, *J* 1.9, C(11)*H*), 8.41 (1H, dd, *J* 8.5, 1.9, C(9)*H*); δ_C (125 MHz, C_6D_6) 9.1 (C(α)*Me*), 23.5 (*C*(3)), 25.8 (*C*(5)), 31.9 (*C*(4)), 39.4 (*C*(3a)), 41.7 (*C*(6)), 47.2 (*C*(2)), 51.1 (O*Me*), 52.5 (*C*(α)), 58.7 (*C*(3b)), 60.4 (*C*(11b)), 110.2 (*C*(8)), 116.3, 119.3, 126.4 (*Ar*, *Ph*), 131.5 (*C*(9)), 133.9 (*C*(11)), 145.0, 148.2 (*C*(7a), *Ar*, *Ph*), 167.4 (*C*O_2Me); *m*/*z* (ESI$^+$) 377 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{29}N_2O_2^+$ ([M+H]$^+$) requires 377.2224; found 377.2210.

4.37. *tert*-Butyl (3*S*,α*R*)-3-[*N*-allyl-*N*-(α-methyl-4″-methoxybenzyl)amino]-3-(2′-*N*,*N*-diallylaminophenyl)propanoate 46

Following *general procedure 1*, (*R*)-*N*-allyl-*N*-(α-methyl-*p*-methoxybenzyl)amine[31] (4.86 g, 25.4 mmol, >99:1 er), BuLi (2.5 M in hexanes, 10.2 mL, 25.4 mmol) and **12** (4.75 g, 15.9 mmol, >99:1 dr) were reacted in THF (150 mL) to give **46** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 83:17) gave **46** as a yellow oil (6.90 g, 89%, >99:1 dr); $[\alpha]_D^{20}$ +19.9 (*c* 1.3, $CHCl_3$); ν_{max} (ATR) 3074, 2977, 2932, 2834 (C–H), 1727 (C=O), 1640, 1610 (C=C); δ_H (400 MHz, $CDCl_3$) 1.19 (3H, d, *J* 6.8, C(α)*Me*), 1.34 (9H, s, C*Me*$_3$), 2.54 (1H, dd, *J* 15.4, 6.1, C(2)H_A), 2.88 (1H, dd, *J* 15.4, 8.2, C(2)H_B), 3.11–3.20 (1H, m, NC$H_A$$H_B$CH=$CH_2$), 3.29–3.37 (1H, m, NC$H_A$$H_B$CH=$CH_2$), 3.49–3.67 (4H, m, N(C$H_2$CH=$CH_2$)$_2$), 3.79 (3H, s, O*Me*), 3.90 (1H, q, *J* 6.8, C(α)*H*), 4.89–5.19 (7H, m, C(3)*H*, NCH_2CH=CH_2, N(CH_2CH=CH_2)$_2$), 5.70–5.91 (3H, m, NCH_2C*H*=CH_2, N(CH_2C*H*=CH_2)$_2$), 6.81 (2H, d, *J* 8.9, C(3″), C(5″)), 7.06–7.14 (2H, m, *Ar*), 7.16–7.24 (1H, app t, *J* 7.6, *Ar*), 7.27 (2H, d, *J* 8.9, C(2″), C(6″)), 7.53 (1H, dd, *J* 7.9, 1.7, *Ar*); δ_C (100 MHz, $CDCl_3$) 15.7 (C(α)*Me*), 28.0 (C*Me*$_3$), 40.4 (*C*(2)), 49.0 (NCH_2CH=CH_2), 54.5 (*C*(3)), 55.2 (O*Me*), 55.7 (*C*(α)), 57.0 (N(CH_2CH=CH_2)$_2$), 80.0 (*C*Me$_3$), 113.1 (*C*(3″), *C*(5″)), 114.3 (NCH_2CH=*C*H_2), 117.6 (N(CH_2CH=*C*H_2)$_2$), 123.7, 124.1, 127.0 (*Ar*), 128.8 (*C*(2″), *C*(6″)), 128.9 (*Ar*), 135.0 (NCH_2*C*H=CH$_2$), 137.2, 139.9 (*Ar*), 140.1 (N(CH_2*C*H=CH_2)$_2$), 150.0 (*Ar*), 158.1 (*C*(4″)), 171.7 (*C*(1)); *m*/*z* (ESI$^+$) 513 ([M+Na]$^+$, 55%), 491 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{43}N_2O_3^+$ ([M+H]$^+$) requires 491.3268; found 491.3253.

4.38. *tert*-Butyl (2*R*,3*S*,α*R*)-2-(2′-methoxy-2′-oxoethyl)-3-[*N*-allyl-*N*-(α-methyl-4‴-methoxybenzyl)amino]-3-(2″-*N*,*N*-diallylaminophenyl)propanoate 47

Following *general procedure 2*, ^{i}Pr$_2$NH (7.72 mL, 55.1 mmol), BuLi (2.5 M in hexanes, 22.0 mL, 55.1 mmol), **46** (18.0 g, 36.7 mmol, >99:1 dr) and methyl bromoacetate (10.4 mL, 110 mmol) were reacted in THF (250 mL) to give **47** in >95:5 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave **47** as a yellow oil (8.63 g, 42%, >99:1 dr); $[\alpha]_D^{20}$ +12.3 (*c* 1.4, $CHCl_3$); ν_{max} (ATR) 3074, 2977, 2835 (C–H), 1728 (C=O), 1640, 1611 (C=C); δ_H (400 MHz, $CDCl_3$) 1.02 (3H, d, *J* 6.6, C(α)*Me*), 1.51 (9H, s, C*Me*$_3$), 2.20 (1H, dd, *J* 15.5, 3.2, C(1′)H_A), 2.50 (1H, dd, *J* 15.5, 11.5, C(1′)H_B), 3.10–3.26 (2H, m, NCH_2CH=CH_2), 3.48–3.58 (3H, m, C(2)*H*, N(C$H_A$$H_B$CH=$CH_2$)$_2$), 3.60 (3H, s, C$O_2$*Me*), 3.58–3.68 (2H, m, N(C$H_A$$H_B$CH=$CH_2$)$_2$), 3.78 (3H, s, ArO*Me*), 4.11 (1H, q, *J* 6.6, C(α)*H*), 4.76–4.89 (2H, m, NCH_2CH=CH_2), 5.02 (1H, d, *J* 11.9, C(3)*H*), 5.11–5.22 (4H, m, N(CH_2CH=CH_2)$_2$), 5.60–5.73 (1H, m, NCH_2C*H*=CH_2), 5.81–5.95 (2H, m, N(CH_2C*H*=CH_2)$_2$), 6.66 (2H, d, *J* 8.8, C(3‴)*H*, C(5‴)*H*), 7.10–7.21 (4H, m, C(2‴)*H*, C(6‴)*H*, *Ar*), 7.24–7.30 (1H, m, *Ar*), 7.37 (1H, dd, *J* 7.8, 1.5, *Ar*); δ_C (100 MHz, $CDCl_3$) 18.5 (C(α)*Me*), 28.1 (C*Me*$_3$), 35.9 (*C*(1′)), 46.6 (CO_2*Me*), 49.8 (NCH_2CH=CH_2), 51.6 (*C*(2)), 55.2 (O*Me*), 55.9 (*C*(α)), 57.3 (N(CH_2CH=CH_2)$_2$), 57.4 (*C*(3)), 80.7 (*C*Me$_3$), 112.9 (*C*(3″), *C*(5″)), 114.6 (NCH_2CH=*C*H_2), 118.4 (N(CH_2CH=*C*H_2)$_2$), 124.4, 124.5, 127.6 (*Ar*), 129.0 (*C*(2″), *C*(6″)), 134.3 (N(CH_2*C*H=CH_2)$_2$), 134.7, 137.4 (*Ar*), 138.9 (NCH_2*C*H=CH$_2$), 151.4 (*Ar*), 158.0 (*C*(4″)), 172.1, 173.7 (*C*(1), *C*(2′)); *m*/*z* (ESI$^+$) 585 ([M+Na]$^+$, 40%), 563 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{34}H_{47}N_2O_5^+$ ([M+H]$^+$) requires 563.3479; found 563.3458.

4.39. (3a*R*,9b*S*,α*R*)-*N*(1)-(α-Methyl-4′-methoxybenzyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinolin-2,4-dione 49

Step 1: $Pd(PPh_3)_4$ (112 mg, 98 μmol) was added to a stirred, degassed solution of **47** (1.10 g, 1.95 mmol, >99:1 dr) and DMBA (2.74 g, 17.6 mmol) in degassed CH_2Cl_2 (30 mL) under argon and the resultant mixture was stirred at 35 °C for 16 h. Additional $Pd(PPh_3)_4$ (112 mg, 98 μmol) was then added and the reaction mixture was stirred at 35 °C for 16 h. The reaction mixture was then concentrated in vacuo and the residue was dissolved in Et_2O (50 mL). The resultant solution was washed with satd aq K_2CO_3 solution (2×20 mL) and the combined aqueous layers were extracted with Et_2O (2×20 mL). The combined organic extracts were then washed with 3.0 M aq HCl (3×20 mL). The combined aqueous layers were basified with 2.0 M aq NaOH until pH>10 was achieved, then extracted with $CHCl_3$/IPA (3:1, 3×20 mL). The combined organic extracts were then dried and concentrated in vacuo to give **48** as a yellow oil (755 mg, >99:1 dr); δ_H (400 MHz, $CDCl_3$) [selected peaks] 2.19 (1H, dd, *J* 16.9, 4.6, C(1′)H_A), 2.43 (1H, dd, *J* 16.9, 4.4, C(1′)H_B), 3.40 (1H, app dt, *J* 9.7, 4.4, C(2)*H*), 6.51 (1H, dd, *J* 7.9, 1.0, *Ar*), 6.62 (1H, td, *J* 7.4, 1.0, *Ar*), 6.78 (2H, d, *J* 8.6, C(3‴)*H*, C(5‴)*H*), 6.90 (1H, dd, *J* 7.5, 1.4, *Ar*), 7.03 (1H, td, *J* 7.6, 1.5, *Ar*), 7.11 (2H, d, *J* 8.6, C(2‴)*H*, C(6‴)*H*).

Step 2: Following *general procedure 4*, a solution of $PhCO_2H$ (47 mg, 0.39 mmol) and **48** (755 mg, >98:2 dr) in PhMe (10 mL) was heated at reflux for 16 h. Purification via flash column chromatography (eluent CH_2Cl_2/MeOH, 95:5) gave **49** as a pale yellow solid (341 mg, 52% from **47**, >99:1 dr); mp 108–112 °C; $[\alpha]_D^{20}$ +61.8 (*c* 1.1, $CHCl_3$); ν_{max} (ATR) 3216, 3063, 2933, 2922 (C–H), 1682 [C=O (γ-lactam)], 1615 [C=O (δ-lactam)]; δ_H (400 MHz, $CDCl_3$) 1.00 (3H, d, *J* 7.3, C(α)*Me*), 2.78 (1H, dd, *J* 16.4, 8.1, C(3)H_A), 3.05–3.13 (1H, m, C(3a)*H*), 3.28 (1H, d, *J* 16.4, C(3)H_B), 3.81 (3H, s, O*Me*), 4.69 (1H, d, *J* 5.6, C(9b)*H*), 5.43 (1H, q, *J* 7.3, C(α)*H*), 6.36 (1H, d, *J* 7.6, *Ar*), 6.83–7.04 (6H, m, C(2′)*H*, C(3′)*H*, C(5′)*H*, C(6′)*H*, *Ar*), 7.26–7.33 (1H, m, *Ar*), 10.06 (1H, s, N(5)*H*); δ_C (100 MHz, $CDCl_3$) 16.8 (C(α)*Me*), 34.3 (*C*(3)), 38.5 (*C*(3a)), 48.5 (*C*(α)), 55.3 (O*Me*), 57.6 (*C*(9b)), 113.8 (*C*(3′), *C*(5′)), 116.0, 117.4, 122.6 (*Ar*), 128.7 (*C*(2′), *C*(6′)), 130.7, 131.0, 131.6, 137.7 (*Ar*), 158.7 (*C*(4′)), 171.0, 173.6 (*C*(2), *C*(4)); *m*/*z* (ESI$^+$) 695 ([2M+Na]$^+$, 100%), 359 ([M+Na]$^+$, 20%); HRMS (ESI$^+$) $C_{20}H_{20}N_2NaO_3^+$ ([M+Na]$^+$) requires 359.1366; found 359.1362.

4.40. (3a*R*,9b*S*,α*R*)-*N*(1)-(α-Methyl-4'-methoxybenzyl)-*N*(5)-(*tert*-butoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinolin-2,4-dione 50

Method A: Boc_2O (243 mg, 1.12 mmol) was added to a solution of **49** (341 mg, 1.01 mmol, >99:1 dr), Et_3N (0.28 mL, 2.02 mmol) and DMAP (12 mg, 0.10 mmol) in CH_2Cl_2 (20 mL) and the resultant mixture was heated at 35 °C for 16 h. The reaction mixture was then washed with 1.0 M aq HCl (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (10 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (10 mL) and brine (10 mL), then dried and concentrated in vacuo. Purification via recrystallisation (PhMe) gave **50** as a white solid (345 mg, 78%, >99:1 dr); $C_{25}H_{28}N_2O_5$ requires C, 68.8; H, 6.5; N, 6.4%; found C, 68.8; H, 6.6; N, 6.5%; mp 162–167 °C; $[\alpha]_D^{20}$ +49.0 (*c* 1.04, $CHCl_3$); ν_{max} (ATR) 2980, 2936, 2837 (C–H), 1767 [C=O (carbamate)], 1691 (C=O [γ lactam]); δ_H (400 MHz, $CDCl_3$) 1.00 (3H, d, *J* 7.1, C(α)*Me*), 1.59 (9H, s, C*Me*$_3$), 2.69 (1H, dd, *J* 16.4, 7.5, C(3)H_A), 3.04–3.12 (1H, app t, *J* 5.6, C(3a)*H*), 3.25 (1H, d, *J* 16.4, C(3)H_B), 3.81 (3H, s, O*Me*), 4.59 (1H, d, *J* 5.6, C(9b)*H*), 5.42 (1H, q, *J* 7.1, C(α)*H*), 6.34 (1H, d, *J* 6.8, *Ar*), 6.82–7.00 (6H, m, C(2′)*H*, C(3′)*H*, C(5′)*H*, C(6′)*H*, *Ar*), 7.33 (1H,

app td, *J* 7.8, 1.3, *Ar*); δ_C (100 MHz, $CDCl_3$) 16.9 (C(α)*Me*), 27.6 (C*Me*$_3$), 34.6 (*C*(3)), 39.5 (*C*(3a)), 48.4 (*C*(α)), 55.3 (O*Me*), 57.4 (*C*(9b)), 85.8 (*C*Me$_3$), 113.8 (*C*(3′), *C*(5′)), 116.1, 118.7, 123.7 (*Ar*), 128.6 (*C*(2′), *C*(6′)), 130.5, 130.9, 132.0, 137.0 (*Ar*), 156.8 (NCO), 158.8 (*C*(4′)), 167.7, 173.2 (*C*(2), *C*(4)); *m*/*z* (ESI$^+$) 895 ([2M+Na]$^+$, 100%), 459 ([M+Na]$^+$, 30%); HRMS (ESI$^+$) $C_{25}H_{28}N_2NaO_5^+$ ([M+Na]$^+$) requires 459.1890; found 459.1885.

4.41. (3a*R*,4*R*,9b*S*,α*R*)- or (3a*R*,4*S*,9b*S*,α*R*)-*N*(1)-(α-Methyl-4′-methoxybenzyl)-4-hydroxy-*N*(5)-(*tert*-butoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinolin-2-one 51

$LiAl(O^tBu)_3H$ (5.97 g, 23.4 mmol) was added to a stirred solution of **50** (6.83 g, 15.6 mmol, >99:1 dr) in THF (150 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 1 h. H_2O (2.0 mL) was then added, the reaction mixture was diluted with EtOAc (50 mL) and stirred at rt for 30 min, then filtered through Celite® (eluent EtOAc/Et_3N, 100:1, 300 mL), dried and concentrated in vacuo to give **51** as a colourless foam (6.86 g, quant, >99:1 dr);[46] $[\alpha]_D^{20}$ +45.9 (*c* 1.0, $CHCl_3$); ν_{max} (ATR) 3299 (O–H), 2976, 2934, 2837 (C–H), 1695 [C=O (γ-lactam, carbamate)]; δ_H (500 MHz, $CDCl_3$) 0.93 (3H, d, *J* 7.3, C(α)*Me*), 1.51 (9H, s, C*Me*$_3$), 2.60 (1H, d, *J* 15.1, C(3)H_A), 2.82–2.94 (2H, m, C(3)H_B, C(3a)*H*), 3.84 (3H, s, O*Me*), 4.48 (1H, d, *J* 6.9, C(9b)*H*), 5.39 (1H, q, *J* 7.3, C(α)*H*), 5.84 (1H, s, C(4)*H*), 6.47 (1H, d, *J* 7.3, *Ar*), 6.88 (2H, d, *J* 8.5, C(3′)*H*, C(5′)*H*), 6.96–7.02 (3H, m, C(2′)*H*, C(6′)*H*, *Ar*), 7.29–7.69 (2H, m, *Ar*); δ_C (125 MHz, $CDCl_3$) 16.8 (C(α)*Me*), 28.4 (C*Me*$_3$), 36.5 (*C*(3)), 42.4 (*C*(3a)), 49.3 (*C*(α)), 55.4 (O*Me*), 56.8 (*C*(9b)), 82.1, 82.2 (*C*(4), *C*Me$_3$), 113.6 (*C*(3′), *C*(5′)), 124.3, 125.9, 128.3 (*Ar*), 129.0 (*C*(2′), *C*(6′)), 129.3, 130.6, 130.7, 137.3 (*Ar*), 152.8 (NCO), 158.8 (*C*(4′)), 173.4 (*C*(2)); *m*/*z* (ESI$^+$) 461 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{30}N_2NaO_5^+$ ([M+Na]$^+$) requires 461.2047; found 461.2037.

4.42. (3a*S*,4*S*,9b*S*,α*R*)-*N*(1)-[α-Methyl-4″-methoxybenzyl]-4-(2′-methoxy-2′-oxoethyl)-*N*(5)-(*tert*-butoxycarbonyl)-2,3,3a,4,5,9b-hexahydropyrrolo[3,2-*c*]quinolin-2-one 52 and (3a*S*,4*R*,9b*S*,α*R*)-*N*(1)-[α-methyl-4″-methoxybenzyl]-4-(2′-methoxy-2′-oxoethyl)-*N*(5)-(*tert*-butoxycarbonyl)-2,3,3a,4,5,9b-hexahydropyrrolo[3,2-*c*]quinolin-2-one 53

NaH (60% w/w in mineral oil, 636 mg, 15.9 mmol) was added to a stirred solution of **54** (3.34 g, 15.9 mmol, >99:1 dr) in THF (50 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 10 min. A solution of **51** (4.65 g, 10.6 mmol) in THF (50 mL) at 0 °C was added and the resultant mixture was stirred at 0 °C for 2 h. H_2O (1 mL) was then added, the reaction mixture was diluted with brine (50 mL), and the aqueous layer was extracted with EtOAc (50 mL). The combined organic extracts were dried and concentrated in vacuo to give a 24:76 mixture of **52** and **53**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc/Et_3N, 50:50:1) gave **53** as a colourless oil (3.54 g, 67%, >99:1 dr); $[\alpha]_D^{20}$ −38.5 (*c* 1.0, $CHCl_3$); ν_{max} (ATR) 2979, 2935, 2838 (C–H), 1738 [C=O (ester)], 1696 [C=O (γ-lactam, carbamate)]; δ_H (400 MHz, $CDCl_3$) 1.38 (3H, d, *J* 7.1, C(α)*Me*), 1.47 (9H, s, C*Me*$_3$), 2.31 (2H, app d, *J* 8.6, C(3)H_2), 2.39 (1H, dd, *J* 15.2, 7.1, C(1′)H_A), 2.53–2.69 (1H, m, C(1′)H_B), 3.04–3.16 (1H, m, C(3a)*H*), 3.65 (3H, s, CO_2Me), 3.82 (3H, s, ArO*Me*), 4.36 (1H, d, *J* 7.8, C(9b)*H*), 4.60 (1H, br s, C(4)*H*), 5.54 (1H, q, *J* 7.1, C(α)*H*), 6.88 (2H, d, *J* 8.6, C(3″)*H*, C(5″)*H*), 7.05 (1H, d, *J* 7.3, *Ar*), 7.11 (1H, app td, *J* 7.3, 1.3, *Ar*), 7.17 (2H, d, *J* 8.6, C(2″)*H*, C(6″)*H*), 7.30 (1H, app td, *J* 7.6, 1.4, *Ar*), 7.37 (1H, d, *J* 7.8, *Ar*); δ_C (100 MHz, $CDCl_3$) 18.0 (C(α)*Me*), 28.2 (C*Me*$_3$), 32.5 (*C*(3)), 36.2 (*C*(1′)), 40.8 (*C*(3a)), 50.3 (*C*(α)), 51.9 (CO_2Me), 52.3 (*C*(4)), 55.2 (ArO*Me*), 56.5 (*C*(9b)), 81.4 (*C*Me$_3$), 113.9 (*C*(3″), *C*(5″)), 124.9, 126.3, 128.0, 128.1 (*Ar*), 128.4 (*C*(2″), *C*(6″)), 130.7, 132.5, 153.2 (*Ar*, NCO), 158.9 (*C*(4″)), 171.2, 174.5 (*C*(2), *C*(2′)); *m*/*z* (ESI$^+$) 517 ([M+Na]$^+$, 100%), 495 ([M+H]$^+$, 50%); HRMS (ESI$^+$) $C_{28}H_{34}N_2NaO_6^+$ ([M+Na]$^+$) requires 517.2309; found 517.2310. Further elution gave **52** as a colourless oil (1.03 g, 20%, >99:1 dr); $[\alpha]_D^{20}$+70.5 (*c* 1.45, $CHCl_3$); ν_{max} (ATR) 2975, 2936, 2838 (C–H), 1738 (C=O, [ester]), 1695 [C=O (γ-lactam, carbamate)], 1609 [C=O (carbamate)]; δ_H (400 MHz, C_6D_6) 1.02 (3H, d, *J* 7.3, C(α)*Me*), 1.55 (9H, s, C*Me*$_3$), 1.89 (1H, dd, *J* 15.4, 7.3, C(1′)H_A), 1.97 (1H, dd, *J* 15.4, 8.1, C(1′)H_B), 2.14–2.25 (1H, m, C(3a)*H*), 2.67 (1H, dd, *J* 17.2, 9.6, C(3)H_A), 2.72–2.82 (1H, m, C(3)H_B), 3.38 (3H, s, CO_2Me), 3.52 (3H, s, ArO*Me*), 4.17 (1H, *J* 7.8, C(9b)*H*), 5.04 (1H, br s, C(4)*H*), 5.70 (1H, q, *J* 7.3, C(α)*H*), 6.50 (1H, dd, *J* 7.6, 1.3, C(9)*H*), 6.87 (1H, dd, *J* 7.6, 1.0, C(8)*H*), 6.91 (2H, d, *J* 8.8, C(3″)*H*, C(5″)*H*), 7.05 (2H, d, *J* 8.8, C(2″)*H*, C(6″)*H*), 7.19 (1H, app td, *J* 7.8, 1.5, C(7)*H*), 7.53 (1H, br s, C(6)*H*); δ_C (100 MHz, C_6D_6) 17.0 (C(α)*Me*), 28.2 (C*Me*$_3$), 38.7 (*C*(3)), 39.2 (*C*(1′)), 40.3 (*C*(3a)), 49.4, 51.1 (O*Me*, *C*(α)), 53.5, 54.9, 56.6 (*C*(4), *C*(9b), O*Me*), 80.9 (*C*Me$_3$), 113.9 (*C*(3″), *C*(5″)), 124.3 (*C*(8)), 127.5 (*C*(6)), 129.0 (*C*(7)), 129.3 (*C*(2″), *C*(6″)), 130.2 (*C*(9)), 130.4, 131.7, 139.3, 152.9 (*Ar*, NCO), 159.2 (*C*(4″)), 170.3, 173.1 (*C*(2), *C*(2′)); *m*/*z* (ESI$^+$) 989 ([2M+H]$^+$, 100%), 517 ([M+Na]$^+$, 100%), 495 ([M+H]$^+$, 35%); HRMS (ESI$^+$) $C_{28}H_{34}N_2NaO_6^+$ ([M+Na]$^+$) requires 517.2309; found 517.2307.

4.43. (3a*R*,4*S*,9b*S*)-4-(2′-Methoxy-2′-oxoethyl)-*N*(5)-(*tert*-butoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinolin-2-one 55

Following *general procedure 5*, reaction of CAN (1.55 g, 2.84 mmol) in H_2O (10 mL) and **52** (467 mg, 0.95 mmol, >99:1 dr) in MeCN (10 mL) gave **55** in >99:1 dr. Purification via flash column chromatography (eluent $CHCl_3$/MeOH, 95:5) gave 4-methoxyacetophenone as a yellow oil (92 mg, 65%). Further elution gave **55** as a yellow oil (195 mg, 57%, >99:1 dr); $[\alpha]_D^{20}$ +32.1 (*c* 1.1, $CHCl_3$); ν_{max} (ATR) 3227 (N–H), 2977 (C–H), 1738 [C=O (ester)], 1696 [C=O (γ-lactam, carbamate)]; δ_H (400 MHz, C_6D_6) 1.45 (9H, s, C*Me*$_3$), 2.10 (1H, dd, *J* 15.2, 6.3, C(1′)H_A), 2.28 (1H, dd, *J* 15.2, 8.6, C(1′)H_B), 2.41–2.57 (3H, m, C(3)H_2, C(3a)*H*), 3.40 (3H, s, O*Me*), 4.38 (1H, d, *J* 7.6, C(9b)*H*), 5.18 (1H, app br t, *J* 7.2, C(4)*H*), 6.94 (1H, app td, *J* 7.6, 1.2, C(8)*H*), 7.10 (1H, app td, *J* 7.6, 1.2, C(7)*H*), 7.28 (1H, dd, *J* 7.6, 1.2, C(9)*H*), 7.74 (1H, br s, C(6)*H*), 8.73 (1H, s, N(1)*H*); δ_C (100 MHz, C_6D_6) 28.1 (C*Me*$_3$), 34.1 (*C*(3)), 36.8 (*C*(1′)), 38.8 (*C*(3a)), 51.3 (O*Me*), 52.1, 52.1 (*C*(4), *C*(9b)), 81.1 (*C*Me$_3$), 125.1 (*C*(8)), 126.2 (*C*(6)), 127.9 (*C*(7)), 129.4 (*Ar*), 129.6 (*C*(9)), 135.5 (*Ar*), 153.7 (NCO), 170.6, 176.7 (*C*(2), *C*(2′)); *m*/*z* (ESI$^+$) 383 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{24}N_2NaO_5^+$ ([M+Na]$^+$) requires 383.1577; found 383.1574.

4.44. (3a*R*,4*S*,9b*S*)-4-(2′-Hydroxyethyl)-*N*(5)-(*tert*-butoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline borane complex 56

BH_3·THF (1.0 M in THF, 5.70 mL, 5.70 mmol) was added to a solution of **55** (172 mg, 0.47 mmol, >99:1 dr) in THF (10 mL) at 0 °C. The resultant mixture was heated at reflux for 4 h then allowed to cool to rt before being cooled to 0 °C. Satd aq K_2CO_3 (5 mL) was added and the resultant mixture was heated at 70 °C for 1 h then allowed to cool to rt. The reaction mixture was washed with brine (2×20 mL) and the combined aqueous washings were extracted EtOAc (2×20 mL). The combined organic extracts were then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc/Et_3N, 50:50:1) gave **56** as a colourless foam (86 mg, 57%, >99:1 dr); $[\alpha]_D^{20}$ +55.2 (*c* 1.4, $CHCl_3$); ν_{max} (ATR) 3465 (N–H), 3193 (O–H), 2975, 2936, 2880 (C–H), 2361, 2270 (B–H), 1684 [C=O (carbamate)]; δ_H (400 MHz, $CDCl_3$) 1.30–1.42 (1H, m, C(1′)H_A), 1.52 (9H, s, C*Me*$_3$), 1.45–1.63 (1H, m, C(1′)H_B), 1.77 (1H, app tt, *J* 10.1, 2.8, C(3)H_A), 2.26–2.39 (1H, m, C(3)H_B), 2.81 (1H, dd, *J* 17.8, 16.1, C(2)H_A), 2.86–2.95 (1H, m, C(3a)*H*), 3.22–3.34 (1H, m, C(2)H_B), 3.36–3.51 (2H, m, C(2′)H_2), 4.04 (1H, br s, N(1)*H*), 4.25 (1H, dd, *J* 9.6, 5.8, C(9b)*H*), 4.63 (1H, dd, *J* 11.7, 2.9, C(4)*H*), 7.13 (1H, app td, *J* 7.5, 0.9, C(8)*H*), 7.28 (1H, app td,

J 7.8, 1.2, C(7)*H*), 7.39 (1H, br s, C(6)*H*), 7.61 (1H, dd, *J* 7.7, 1.2, C(9)*H*); δ_C (100 MHz, $CDCl_3$) 28.2 (C*Me*$_3$), 30.4 (*C*(3)), 34.3 (*C*(1′)), 43.6 (*C*(3a)), 52.8 (*C*(4)), 54.0 (*C*(2)), 58.6 (*C*(2′)), 63.6 (*C*(9b)), 82.4 (*C*Me$_3$), 124.9, 125.0 (*C*(6), *C*(8)), 126.3 (*Ar*), 129.2 (*C*(7)), 130.4 (*C*(9)), 135.8 (*Ar*) 155.0 (NCO); δ_B (^{11}B, 160 MHz, $CDCl_3$) −14.9; *m*/*z* (ESI$^+$) 687 ([2M+Na]$^+$, 100%), 319 ([M−BH_2]$^+$, 50%); HRMS (ESI$^+$) $C_{18}H_{29}BN_2NaO_3^+$ ([M+Na]$^+$) requires 355.2163; found 355.2162.

4.45. (3a*R*,4*S*,9b*S*)-4-(2′-Hydroxyethyl)-*N*(5)-(*tert*-butoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 57

Step 1: Following *general procedure 5*, reaction of CAN (2.22 g, 4.06 mmol) in H_2O (13 mL) and **52** (669 mg, 1.35 mmol, >99:1 dr) in MeCN (13 mL) gave **55** as a yellow oil (589 mg, >99:1 dr).

Step 2: BH_3·THF (1.0 M in THF, 16.0 mL, 16.0 mmol) was added to a solution of **55** (589 mg, >99:1 dr) in THF (50 mL) at 0 °C. The resultant mixture was heated at reflux for 4 h then allowed to cool to rt before being cooled to 0 °C and satd aq K_2CO_3 (5 mL) was added. The resultant mixture was heated at 60 °C for 1 h then allowed to cool to rt and washed with satd aq K_2CO_3 (2×10 mL). The combined aqueous layers were extracted with EtOAc (20 mL) and the combined organic extracts were dried and concentrated in vacuo to give **56** (831 mg).

Step 3: Pd/C (10% w/w, 60 mg) was added to a solution of **56** (584 mg) in MeOH (15 mL) and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then filtered through a pad of Celite® (eluent MeOH/Et_3N, 100:1) and the filtrate was concentrated in vacuo. Purification via flash column chromatography (eluent CH_2Cl_2/MeOH/Et_3N, 95:5:1) gave **57** as a colourless oil (197 mg, 57% from **52**, >99:1 dr); $[\alpha]_D^{20}$ +50.9 (*c* 1.0, $CHCl_3$); ν_{max} (ATR) 3377 (O−H, N−H), 2974, 2934, 2878, 2730 (C−H), 1694 (C=O); δ_H (400 MHz, $CDCl_3$) 1.40−1.52 (1H, m, C(1′)H_A), 1.48 (9H, s, C*Me*$_3$) 1.54−1.63 (1H, m, C(1′)H_B), 1.66−1.79 (1H, m, C(3)H_A), 2.18−2.28 (1H, m, C(3)H_B), 2.68 (1H, app q, *J* 8.8, C(3a)*H*), 2.87−2.98 (1H, m, C(2)H_A), 2.97−3.07 (1H, m, C(2)H_B), 3.40−3.50 (2H, m, C(2′)H_2), 4.57 (1H, d, *J* 9.4, C(9b)*H*), 4.66 (1H, dd, *J* 11.5, 3.4, C(4)*H*), 7.08 (1H, app t, *J* 7.4, C(8)*H*), 7.21 (1H, app td, *J* 7.4, 1.3, C(7)*H*), 7.38 (1H, br d, *J* 7.4, C(6)*H*), 7.43 (1H, d, *J* 7.4, C(9)*H*); δ_C (100 MHz, $CDCl_3$) 28.3 (C*Me*$_3$), 30.6 (*C*(3)), 34.6 (*C*(1′)), 43.2 (*C*(3a)), 44.9 (*C*(2)), 52.6 (*C*(4)), 55.9 (*C*(9b)), 58.7 (*C*(2′)), 82.1 (*C*Me$_3$), 125.0, 127.1, 128.5, 130.0, 136.1 (*Ar*) 155.0 (NCO); *m*/*z* (ESI$^+$) 341 ([M+Na]$^+$, 95%), 319 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{26}N_2NaO_3^+$ ([M+Na]$^+$) requires 341.1836; found 341.1837.

4.46. (*S*,*S*,*S*)-*N*(1),*N*(5)-(Bis-*tert*-butoxycarbonyl)-4-[2′-(4″-toluenesulfonyloxy)ethyl]-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 59

Step 1: Boc_2O (147 mg, 0.67 mmol), DMAP (8 mg, 61 μmol) and Et_3N (0.26 mL, 1.83 mmol) were added sequentially to a stirred solution of **57** (195 mg, 0.61 mmol, >99:1 dr) in CH_2Cl_2 (10 mL) and the resultant mixture was stirred at 35 °C for 16 h. The reaction mixture was then diluted with CH_2Cl_2 (20 mL) and washed with 1.0 M aq HCl (10 mL). The aqueous layer was extracted with $CHCl_3$/IPA (3:1, 2×20 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (10 mL) and brine (10 mL), then dried and concentrated in vacuo to give **58** (178 mg, >99:1 dr).

Step 2: TsCl (140 mg, 0.73 mmol), DMAP (8 mg, 61 μmol) and Et_3N (0.26 mL, 1.83 mmol) were added sequentially to a stirred solution of **58** (178 mg, >99:1 dr) in CH_2Cl_2 (10 mL) and the resultant mixture was stirred at 35 °C for 16 h. The reaction mixture was then diluted with CH_2Cl_2 (20 mL) and washed with 1.0 M aq HCl (10 mL). The aqueous layer was extracted with $CHCl_3$/IPA (3:1, 2×20 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (10 mL) and brine (10 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O/Et_3N, 80:20:1) gave **59** as a colourless oil (134 mg, 38% from **57**, >99:1 dr); $[\alpha]_D^{20}$ −104 (*c* 1.0, $CHCl_3$); ν_{max} (ATR) 2976, 2932 (C−H), 1691 (C=O); δ_H (400 MHz, PhMe-d_8, 363 K) 1.33−1.55 (2H, C(1′)H_2), 1.47 (9H, s, C*Me*$_3$), 1.49 (9H, s, C*Me*$_3$), 1.58−1.74 (2H, m, C(3)H_2), 1.86−1.95 (1H, m, C(3a)*H*), 2.02 (3H, s, C(4″)*Me*), 3.05−3.15 (1H, m, C(2)H_A), 3.23−3.41 (1H, m, C(2)H_B), 3.82−3.91 (1H, m, C(2′)H_A), 3.92−4.03 (1H, m, C(2′)H_B), 4.57−4.64 (1H, m, C(4)*H*), 5.01 (1H, d, *J* 7.6, C(9b)*H*), 6.87 (2H, d, *J* 8.0, C(3″), C(5″)), 6.94 (1H, app t, *J* 7.4, *Ar*), 6.97−7.06 (1H, m, *Ar*), 7.56 (1H, d, *J* 8.2, *Ar*), 7.69 (2H, d, *J* 8.0, C(2″)*H*, C(6″)*H*), 8.08 (1H, br s, *Ar*); δ_C (100 MHz, PhMe-d_8, 363 K) 21.0 (C(4″)*Me*), 28.1 (*C*(3)), 28.3, 28.6 (2×C*Me*$_3$), 32.2 (*C*(1′)), 42.7 (*C*(3a)), 45.6 (*C*(2)), 52.3 (*C*(4)), 54.6 (*C*(9b)), 67.2 (*C*(2′)), 79.2, 80.9 (2×*C*Me$_3$), 124.5, 125.5, 127.4 (*Ar*), 128.1 (*C*(2″), *C*(6″)), 129.6 (*C*(3″), *C*(5″)), 130.1, 131.0, 135.2, 135.6, 143.9 (*Ar*), 154.2, 155.5 (2×NCO); *m*/*z* (ESI$^+$) 595 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{40}N_2NaO_7S^+$ ([M+Na]$^+$) requires 595.2448; found 595.2445.

4.47. (*S*,*S*,*S*)-*N*(1),*N*(5)-(Bis-*tert*-butoxycarbonyl)-4-(2′-cyanoethyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 60

NaCN (12 mg, 0.23 mmol) was added to a stirred solution of **59** (85 mg, 0.15 mmol, >99:1 dr) in NMP (2 mL) and the resultant mixture was heated at 60 °C for 16 h. The reaction mixture was then diluted with EtOAc (20 mL) and washed with H_2O (2×10 mL). The combined aqueous layers were extracted with EtOAc (2×10 mL) and the combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/EtOAc/Et_3N, 66:34:1) gave **60** as a white foam (45 mg, 70%, >99:1 dr); $[\alpha]_D^{20}$ −127 (*c* 1.1, $CHCl_3$); ν_{max} (ATR) 2976, 2933 (C−H), 2247 (C≡N), 1691 (C=O); δ_H (500 MHz, PhMe-d_8, 363 K) 1.02−1.13 (1H, m, C(1′)H_A), 1.23−1.38 (1H, m, C(1′)H_B), 1.47 (9H, s, C*Me*$_3$), 1.50 (9H, s, C*Me*$_3$), 1.61−1.90 (5H, m, C(3)H_2, C(3a)*H*, C(2′)H_2), 3.05−3.15 (1H, m, C(2)H_A), 3.27−3.40 (1H, m, C(2)H_B), 4.42 (1H, app d, *J* 11.0, C(4)*H*), 4.99 (1H, d, *J* 7.3, C(9b)*H*), 6.95 (1H, app t, *J* 7.6, C(8)*H*), 7.05 (1H, app t, *J* 7.6, C(7)*H*), 7.59 (1H, d, *J* 8.2, C(6)*H*), 8.08 (1H, br s, C(9)*H*); δ_C (125 MHz, PhMe-d_8, 363 K) 14.1 (*C*(2′)), 28.2, 28.3, 28.5, 28.6 (*C*(3), *C*(1′), 2×C*Me*$_3$), 42.8 (*C*(3a)), 45.5 (*C*(2)), 54.6, 54.6 (*C*(4), *C*(9b)), 79.3, 81.2 (2×*C*Me$_3$), 118.3 (*C*(3′)), 124.7 (*C*(8)), 125.6 (*C*(6)), 127.5 (*C*(7)), 129.9 (*C*(9)), 131.0, 135.2 (*C*(5a), *C*(9a)), 154.3, 155.5 (2×NCO); *m*/*z* (ESI$^+$) 450 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{33}N_3NaO_4^+$ ([M+Na]$^+$) requires 450.2363; found 450.2368.

4.48. (*S*,*S*,*S*)-*N*(1),*N*(5)-(Bis-*tert*-butoxycarbonyl)-4-[3′-(*N*-*tert*-butoxycarbonylamino)propyl]-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 61

Boc_2O (45 mg, 0.21 mmol) was added to a stirred solution of $NiCl_2·6H_2O$ (5 mg, 21 μmol) and **60** (45 mg, 0.10 mmol, >99:1 dr) in dry MeOH (3 mL) and the resultant mixture was stirred at 0 °C for 5 min. $NaBH_4$ (55 mg, 1.45 mmol) was then added, during which time a fine black precipitate formed and a gas was evolved. The resultant mixture was allowed to warm to rt over 16 h then DETA (11 μL, 0.10 mmol) was added and the reaction mixture was allowed to stir for 30 min at rt before being concentrated in vacuo. The residue was dissolved in EtOAc (10 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (2×10 mL). The combined aqueous layers were extracted with EtOAc (10 mL) and the combined organic extracts were then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O/Et_3N, 50:50:1) gave **61** as a colourless oil (40 mg, 71%, >99:1 dr); $[\alpha]_D^{20}$ −67.1 (*c* 1.0, $CHCl_3$); ν_{max} (ATR) 3361 (N−H), 2976, 2932 (C−H), 1693 (C=O); δ_H (500 MHz, PhMe-d_8, 363 K) 1.20−1.62

(4H, m, C(1′)H_2, C(2′)H_2), 1.63–1.84 (2H, m, C(3)H_2), 1.44 (9H, s, CMe_3), 1.46 (9H, s, CMe_3), 1.50 (9H, s, CMe_3), 1.99–2.09 (1H, br m, C(3a)*H*), 2.99–3.22 (1H, br m, C(2)H_A), 3.26–3.45 (1H, br m, C(2)H_B), 3.87–4.03 (1H, br m, C(3′)H_A), 4.12–4.22 (1H, br m, C(3′)H_B), 4.37–4.77 (2H, br m, C(4)*H*, N*H*), 4.99–5.22 (1H, br m, C(9b)*H*), 6.85–7.17 (2H, br m, *Ar*), 7.51–7.73 (1H, br m, *Ar*), 7.99–8.23 (1H, br m, *Ar*); δ_C (125 MHz, PhMe-d_8, 363 K) 26.8, 31.6 (*C*(1′), *C*(2′)), 27.9, 28.1, 28.2 (3×CMe_3), 45.2 (*C*(2)), 47.7 (*C*(4)), 52.1 (*C*(9b)), 64.4 (*C*(3′)), 78.2, 78.7, 80.2 (3×CMe_3), 129.8, 130.1, 130.7 (*Ar*), 153.8, 155.4, 155.7 (3×NCO);[47] *m*/*z* (ESI$^+$) 554 ([M+Na]$^+$, 100%), 532 ([M+H]$^+$, 40%); HRMS (ESI$^+$) $C_{29}H_{45}N_3NaO_6^+$ ([M+Na]$^+$) requires 554.3206; found 554.3203.

4.49. (*S*,*S*,*S*)-4-(3′-Aminopropyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline·*x*HCl 62·*x*HCl

A solution of **61** (35 mg, 65 μmol, >99:1 dr) in HCl (1.25 M in MeOH, 4 mL) was stirred at rt for 16 h then was concentrated in vacuo. HCl (1.25 M in MeOH, 2 mL) was added and the resultant mixture was concentrated in vacuo to give **62**·*x*HCl as an amorphous white solid (19 mg, quant, >99:1 dr);[48] $[\alpha]_D^{20}$ −58.0 (*c* 0.2, MeOH); ν_{max} (ATR) 3376 (N–H), 2904, 2745 (C–H); δ_H (500 MHz, MeOH-d_4) 1.84–2.09 (4H, m, C(1′)H_2, C(2′)H_2), 2.15–2.25 (1H, m, C(3)H_A), 2.51–2.62 (1H, m, C(3)H_B), 2.82–2.91 (1H, m, C(3a)*H*), 3.00–3.13 (2H, m, C(3′)H_2), 3.31–3.35 (1H, m, C(4)*H*), 3.40–3.57 (2H, m, C(2)H_2), 4.85 (1H, d, *J* 7.3, C(9b)*H*), 7.22–7.28 (1H, m, *Ar*), 7.32 (1H, d, *J* 7.9, *Ar*), 7.40–7.46 (1H, m, *Ar*), 7.57 (1H, d, *J* 6.3, *Ar*); δ_C (125 MHz, MeOH-d_4) 24.1 (*C*(1′)), 28.3 (*C*(3)), 29.6 (*C*(2′)), 39.5 (*C*(3a)), 40.6 (*C*(3′)), 44.7 (*C*(2)), 54.0 (*C*(4)), 58.4 (*C*(9b)), 120.6, 121.0, 125.6, 131.5, 131.8, 139.5 (*Ar*); *m*/*z* (ESI$^+$) 232 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{22}N_3^+$ ([M+H]$^+$) requires 232.1808; found 232.1815.

4.50. (3a*S*,4*R*,9b*S*,α*R*)-*N*(1)-(α-Methyl-4″-methoxybenzyl)-4-(2′-methoxy-2′-oxoethyl)-*N*(5)-(*tert*-butoxycarbonyl)-8-bromo-2,3,3a,4,5,9b-hexahydropyrrolo[3,2-*c*]quinolin-2-one 72

NaH (60% w/w in mineral oil, 236 mg, 5.90 mmol) was added portionwise to a solution of **54** (1.24 g, 5.90 mmol) in THF (59 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 5 min. A solution of **71** (2.78 g, 5.36 mmol, >99:1 dr) in THF (59 mL) at 0 °C was then added dropwise. The resultant mixture was stirred at 0 °C for 2 h, then H_2O (2 mL) was added. The reaction mixture was then diluted with EtOAc (50 mL) and washed with brine (2×50 mL). The combined aqueous layers were extracted with EtOAc (50 mL) and the combined organic extracts were dried and concentrated in vacuo to give a 50:50 mixture of **67** and **72**. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc/Et_3N, 66:34:1) gave **72** as a colourless oil (1.09 g, 36%, >99:1 dr); $[\alpha]_D^{20}$ −19.7 (*c* 1.0, $CHCl_3$); ν_{max} (ATR) 2977, 2935, 2837 (C–H), 1738 (C=O, [ester]), 1698 (C=O, [carbamate]); δ_H (400 MHz, $CDCl_3$) 1.23 (3H, d, *J* 7.1, C(α)*Me*), 1.38 (9H, s, CMe_3), 2.16–2.46 (3H, m, C(3)H_A, C(1′)H_2), 2.49–2.70 (1H, br s, C(3)H_B), 2.91–3.06 (1H, m, C(3a)*H*), 3.56 (3H, s, CO_2Me), 3.72 (3H, s, ArO*Me*), 4.26 (1H, d, *J* 8.1, C(9b)*H*), 4.39 (1H, br s, C(4)*H*), 5.43 (1H, q, *J* 7.1, C(α)*H*), 6.82 (2H, d, *J* 8.7, C(3″)*H*, C(5″)*H*), 6.93 (1H, br s, C(9)*H*), 7.07 (2H, d, *J* 8.7, C(2″)*H*, C(6″)*H*), 7.19 (1H, d, *J* 8.6, C(6)*H*), 7.32 (1H, dd, *J* 8.6, 2.2, C(7)*H*); δ_C (100 MHz, $CDCl_3$) 18.0 (C(α)*Me*), 28.1 (CMe_3), 32.3 (*C*(1′)), 35.9 (*C*(3)), 40.1 (*C*(3a)), 50.3 (*C*(α)), 51.9 (CO_2Me), 53.0 (*C*(4)), 55.2 (ArO*Me*), 56.5 (*C*(9b)), 81.8 (*C*Me$_3$), 114.0 (*C*(3″), *C*(5″)), 117.8 (*C*(6)), 127.8 (*Ar*), 128.5 (*C*(2″), *C*(6″)), 131.1 (*C*(7)), 131.4 (*C*(9)), 131.7, 132.5, 139.0 (*Ar*), 152.8, 158.9 (*C*(4″), NCO), 171.0, 174.2 (*C*(2), *C*(2′)); *m*/*z* (ESI$^+$) 595 ([M(^{79}Br)+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{33}{}^{79}BrN_2NaO_6^+$ ([M(^{79}Br)+Na]$^+$) requires 595.1414; found 595.1414. Further elution gave **67** as a colourless oil (1.15 g, 38%, >99:1 dr).

4.51. (3a*S*,4*R*,9b*S*)-4-(2′-Hydroxyethyl)-*N*(5)-(*tert*-butoxycarbonyl)-8-bromo-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 74

Step 1: Following *general procedure 5*, reaction of CAN (6.05 g, 11.1 mmol) in H_2O (35 mL) and **72** (2.11 g, 3.68 mmol, >99:1 dr) in MeCN (70 mL) gave **73** as a yellow oil (2.11 g, >99:1 dr); δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.51 (9H, s, CMe_3), 2.20–2.31 (2H, m, C(2)H_A, C(2′)H_A), 3.05–3.15 (1H, m, C(3a)*H*), 4.72 (1H, d, *J* 7.1, C(9b)*H*), 5.04–5.17 (1H, m, C(4)*H*), 6.86 (1H, br s, N*H*), 7.36–7.51 (3H, m, C(6)*H*, C(7)*H*, C(9)*H*).

Step 2: BH_3·THF (1.0 M in THF, 37.0 mL, 37.0 mmol) was added dropwise to a solution of **73** (2.11 g, >99:1 dr) in THF (50 mL) at 0 °C. The resultant mixture was heated at reflux for 4 h then allowed to cool to rt before being cooled further to 0 °C. Satd aq K_2CO_3 (30 mL) and EtOAc (30 mL) were then carefully added and the resultant mixture was heated at 60 °C for 1 h. The reaction mixture was then allowed to cool to rt and washed with satd aq K_2CO_3 (2×30 mL). The combined aqueous layers were extracted with EtOAc (50 mL) and the combined organic extracts were dried and concentrated in vacuo to give a mixture of **74** and **74** BH_3 (831 mg).[49]

Step 3: The residue of **74** and **74** BH_3 (831 mg) was dissolved in MeOH (100 mL) and the resultant mixture was heated at reflux for 48 h, then was allowed to cool to rt and concentrated in vacuo. Purification via flash column chromatography (eluent EtOAc/Et_3N, 100:1) gave **74** as a white foam (770 mg, 53% from **72**, >99:1 dr); $[\alpha]_D^{20}$ −11.5 (*c* 1.0, $CHCl_3$); ν_{max} (ATR) 3315 (O–H, N–H), 2975, 2931, 2879 (C–H), 1692 (C=O); δ_H (400 MHz, $CDCl_3$) 1.11 (1H, m, C(1′)H_A), 1.52 (9H, s, CMe_3), 1.64–1.82 (2H, m, C(3)H_A, C(1′)H_B), 2.02–2.15 (1H, m, C(3)H_B), 2.77–2.88 (1H, m, C(3a)*H*), 2.90–3.00 (1H, m, C(2)H_A), 3.03–3.12 (1H, m, C(2)H_B), 3.40–3.54 (2H, m, C(2′)H_2), 3.97 (1H, d, *J* 8.1, C(9b)*H*), 4.68–4.82 (1H, m, C(4)*H*), 7.23–7.33 (2H, m, C(6)*H*, C(7)*H*), 7.62 (1H, d, *J* 1.3, C(9)*H*); δ_C (100 MHz, $CDCl_3$) 28.3 (CMe_3), 28.6 (*C*(3)), 29.9 (*C*(1′)), 41.2 (*C*(3a)), 45.7 (*C*(2)), 49.3 (*C*(4)) 56.6 (*C*(9b)), 58.7 (*C*(2′)), 82.1 (*C*Me$_3$), 117.4 (*Ar*), 126.4, 129.9 (*C*(6), *C*(7)), 131.4 (*C*(9)), 133.7, 133.8 (*Ar*);[50] *m*/*z* (ESI$^+$) 397 ([M(^{79}Br)+H]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{26}{}^{79}BrN_2O_3^+$ ([M(^{79}Br)+H]$^+$) requires 397.1121; found 397.1114.

4.52. (3a*S*,4*R*,9b*S*)-*N*(1),*N*(5)-(Bis-*tert*-butoxycarbonyl)-4-[2′-(4″-toluenesulfonyloxy)ethyl]-8-bromo-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 75

Step 1: Boc_2O (447 mg, 2.05 mmol), DMAP (23 mg, 0.19 mmol) and Et_3N (0.78 mL, 5.58 mmol) were added sequentially to a solution of **74** (739 mg, 1.86 mmol, >99:1 dr) in CH_2Cl_2 (50 mL) and the resultant mixture was stirred at 35 °C for 16 h. The reaction mixture was then diluted with CH_2Cl_2 (20 mL) and washed with 1.0 M aq HCl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (10 mL) and brine (10 mL), then dried and concentrated in vacuo.

Step 2: The residue (900 mg, >99:1 dr) was dissolved in CH_2Cl_2 (20 mL) and TsCl (390 mg, 2.05 mmol), DMAP (23 mg, 0.19 mmol) and Et_3N (0.78 mL, 5.58 mmol) were added sequentially. The resultant mixture was stirred at 35 °C for 16 h, then diluted with CH_2Cl_2 (20 mL) and washed with 1.0 M aq HCl (20 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (10 mL) and brine (10 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc/Et_3N, 66:34:1) gave **75** as a colourless foam (760 mg, 63% from **74**, >99:1 dr); $[\alpha]_D^{20}$ −91.0 (*c* 1.0, $CHCl_3$); ν_{max} (ATR) 2977, 2932 (C–H), 1694, 1598 (C=O); δ_H (400 MHz, C_6D_6) 0.57–0.92 (2H, br m, C(3)H_2), 0.94–1.16 (2H, br m, C(1′)H_2), 1.38 (18H, s, 2×CMe_3), 1.86 (3H, s, C(4″)*Me*), 2.20–2.46 (1H, br s, C(3a)*H*), 2.83–3.34

(2H, br m, C(2)H_2), 3.90–4.11 (2H, br m, C(2′)H_2), 4.37–4.55 (1H, br m, C(9b)*H*), 4.62 (1H, td, *J* 10.7, 3.5, C(4)*H*), 6.76 (2H, d, *J* 8.2, C(3″)*H*, C(5″)*H*), 6.91–7.12 (1H, br s, *Ar*), 7.18 (1H, br d, *J* 8.3, *Ar*), 7.65 (1H, br s, *Ar*), 7.81 (2H, d, *J* 8.2, C(2″)*H*, C(6″)*H*); δ_C (100 MHz, C_6D_6) 20.8 (C(4″)*Me*), 27.8, 28.0 (2×CMe_3), 30.4 (*C*(1′)), 45.8 (*C*(2)), 48.0 (*C*(4)), 55.7 (*C*(9b)), 67.3 (*C*(2′)) 79.4, 80.7 (2×*C*Me$_3$), 118.5, 128.2, 129.3 (*Ar*), 129.6 (*C*(2″), *C*(6″)), 129.9, 133.9, 134.7, 135.5 (*Ar*), 144.1, 152.9 (2×NCO);[51] *m*/*z* (ESI$^+$) 675 ([M(^{81}Br)+Na]$^+$, 95%), 673 ([M(^{79}Br)+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{39}{}^{79}BrN_2NaO_7S^+$ ([M(^{79}Br)+Na]$^+$) requires 673.1554; found 673.1562.

4.53. (3a*S*,4*R*,9b*S*)-*N*(1),*N*(5)-(Bis-*tert*-butoxycarbonyl)-4-(2′-cyanoethyl)-8-bromo-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]-quinoline 76

NaCN (72 mg, 1.47 mmol) was added to a solution of **75** (639 mg, 0.98 mmol, >99:1 dr) in NMP (4 mL) and the resultant mixture was stirred at 60 °C for 16 h. The reaction mixture was then diluted with EtOAc (30 mL) and washed with H_2O (3×10 mL). The combined aqueous layers were extracted with EtOAc (2×10 mL) and the combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc/Et_3N, 66:34:1) gave **76** as a white foam (430 mg, 87%, >99:1 dr); $[\alpha]_D^{20}$ −119 (*c* 1.0, $CHCl_3$); ν_{max} (ATR) 2977, 2932 (C–H), 2247 (C≡N), 1693 (C=O); δ_H (400 MHz, C_6D_6) 0.53–0.88 (4H, br m, C(3)H_2, C(1′)H_2), 1.38 (18H, s, 2×CMe_3), 1.61–1.74 (1H, m, C(2′)H_A), 1.74–1.89 (1H, m, C(2′)H_B), 2.16–2.42 (1H, br s, C(3a)*H*), 2.87–3.34 (2H, br m, C(2)H_2), 4.46 (1H, td, *J* 11.0, 3.4, C(4)*H*), 4.53–4.74 (1H, br s, C(9b)*H*), 7.10–7.29 (2H, br m, *Ar*), 7.64 (1H, br s, *Ar*); δ_C (100 MHz, C_6D_6) 14.1 (*C*(2′)), 24.6, 26.7 (*C*(3), *C*(1′)), 27.8, 28.0 (2×CMe_3), 43.9 (*C*(3a)), 45.7 (*C*(2)), 50.3 (*C*(4)), 55.7 (*C*(9b)), 79.5, 81.0 (2×*C*Me$_3$), 118.7, 119.1 (*C*(3′), *Ar*), 128.4, 129.2, 130.0, 134.4, 135.4 (*Ar*), 153.2, 154.5 (2×NCO); *m*/*z* (ESI$^+$) 528 ([M(^{79}Br)+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{32}{}^{79}BrN_3NaO_4^+$ ([M(^{79}Br)+Na]$^+$) requires 528.1468; found 528.1469.

4.54. (3a*S*,4*R*,9b*S*)-*N*(1),*N*(5)-(Bis-*tert*-butoxycarbonyl)-4-(2′-cyanoethyl)-8-(methoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 77

Following *general procedure 6*, $Pd(OAc)_2$ (16 mg, 73 μmol), Xantphos (85 mg, 0.15 mmol), **76** (372 mg, 0.73 mmol, >99:1 dr) and Et_3N (5 mL) were reacted in MeOH (1 mL). Resubjection of the crude reaction mixture to the reaction conditions twice more gave **77** as the sole product. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc/Et_3N, 75:25:1) gave **77** as a colourless oil (263 mg, 74%, >99:1 dr); $[\alpha]_D^{20}$ −172 (*c* 1.0, $CHCl_3$); ν_{max} (ATR) 2977, 2934 (C–H), 2247 (C≡N), 1694, 1611 (C=O); δ_H (400 MHz, C_6D_6) 0.51–0.80 (4H, m, C(3)H_2, C(1′)H_2), 1.16 (9H, s, CMe_3), 1.24 (9H, s, CMe_3), 1.52–1.74 (2H, m, C(2′)H_2), 2.23 (1H, br s, C(3a)*H*), 2.71–3.16 (2H, br m, C(2)H_2), 3.29 (3H, s, O*Me*), 4.24–4.38 (1H, m, C(4)*H*), 4.36–4.56 (1H, br s, C(9b)*H*), 7.21 (1H, br s, C(6)*H*), 7.78 (1H, d, *J* 7.8, C(7)*H*), 7.99 (1H, s, C(9)*H*); δ_C (100 MHz, C_6D_6) 14.1 (*C*(2′)), 25.0, 26.9 (*C*(3), *C*(1′)), 27.8, 28.0 (2×CMe_3), 43.9 (*C*(3a)), 45.8 (*C*(2)), 50.6 (*C*(4)), 51.3 (O*Me*), 55.6 (*C*(9b)), 79.5, 81.2 (2×*C*Me$_3$), 119.1 (*C*(3′)), 126.5 (*C*(6)), 127.0 (*C*(9)), 128.2 (*C*(7)), 133.0, 139.6 (*Ar*), 153.0, 154.6 (2×NCO), 166.1 (*C*O$_2$Me); *m*/*z* (ESI$^+$) 508 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{35}N_3NaO_6^+$ ([M+Na]$^+$) requires 508.2418; found 508.2408.

4.55. (3a*S*,4*R*,9b*S*)-*N*(1),*N*(5)-(Di-*tert*-butoxycarbonyl)-4-[3′-(*N*-*tert*-butoxycarbonylamino)propyl]-8-(methoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 78

Boc_2O (195 mg, 0.89 mmol) was added to a solution of $NiCl_2·6H_2O$ (21 mg, 89 μmol) and **77** (217 mg, 0.45 mmol, >99:1 dr) in dry MeOH (5 mL) and the resultant mixture was stirred at 0 °C for 5 min. $NaBH_4$ (237 mg, 6.26 mmol) was then added portionwise over a period of 15 min, during which time a fine black precipitate formed and a gas was evolved. The reaction mixture was stirred at 0 °C for 1 h then DETA (48 μL, 0.45 mmol) was added and the resultant mixture was allowed to stir for 30 min at 0 °C before being concentrated in vacuo. The residue was dissolved in EtOAc (20 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (2×10 mL). The combined aqueous layers were extracted with EtOAc (10 mL) and the combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc/Et_3N, 66:34:1) gave **78** as a colourless oil (218 mg, 83%, >99:1 dr); $[\alpha]_D^{20}$ −151 (*c* 0.98, $CHCl_3$); ν_{max} (ATR) 3368 (N–H), 2977, 2933 (C–H), 1692, 1611 (C=O); δ_H (400 MHz, C_6D_6) 0.79–1.14 (4H, m, C(3)H_2, C(1′)H_2), 1.25–1.70 (2H, br m, C(2′)H_2), 1.37 (9H, s, CMe_3), 1.43 (18H, s, 2×CMe_3), 2.41–2.65 (1H, br s, C(3a)*H*), 2.83–3.43 (4H, br m, C(2)H_2, C(3′)H_2), 3.50 (3H, s, O*Me*), 4.38 (1H, br m, N*H*), 4.49–4.89 (2H, br m, C(4)*H*, C(9b)*H*), 7.42 (1H, br s, C(6)*H*), 8.09 (1H, d, *J* 7.8, C(7)*H*), 8.35 (1H, s, C(9)*H*); δ_C (100 MHz, C_6D_6) 25.1 (*C*(3)), 26.7 (*C*(2′)), 27.9 (CMe_3), 28.0 (*C*(1′)), 28.1, 28.2 (2×CMe_3), 39.9 (*C*(3′)), 46.0 (*C*(2)), 50.9, 51.2 (*C*(4), O*Me*), 55.8 (*C*(9b)), 78.1, 79.4, 80.5 (3×*C*Me$_3$), 126.0 (*C*(6)), 126.6 (*Ar*), 128.1, 128.1 (*C*(7), *C*(9)), 133.3, 140.4 (*Ar*), 153.0, 154.7, 155.6 (3×NCO), 166.1 (*C*O$_2$Me);[52] *m*/*z* (ESI$^+$) 612 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{47}N_3NaO_8^+$ ([M+Na]$^+$) requires 612.3255; found 612.3247.

4.56. (3a*S*,4*R*,9b*S*)-4-(3′-Aminoethyl)-8-(methoxycarbonyl)-2,3,3a,4,5,9b-hexahydropyrrolo[3,2-*c*]-1*H*-quinoline hydrochloride 79·*x*HCl

A solution of **78** (158 mg, 0.27 mmol, >99:1 dr) in HCl (1.25 M in MeOH, 4 mL) was stirred at rt for 6 h then concentrated in vacuo. HCl (1.25 M in MeOH, 2 mL) was then added and the resultant mixture was concentrated in vacuo to give **79**·*x*HCl as an amorphous white solid (105 mg, quant, >99:1 dr); $[\alpha]_D^{20}$ +93.7 (*c* 0.35, MeOH) {lit.[9c] for enantiomer $[\alpha]_D^{20}$ −73.7 (*c* 0.34, MeOH)}; ν_{max} (ATR) 3361, 2948 (N–H), 2361, 2342 (C–H), 1699 (C=O); δ_H (400 MHz, MeOH-d_4) 1.64–1.99 (4H, br m, C(1′)H_2, C(2′)H_2), 1.99–2.13 (1H, m, C(3)H_A), 2.14–2.27 (1H, br m, C(3)H_B), 2.92–3.03 (1H, m, C(3a)*H*), 3.06 (2H, t, *J* 7.1, C(3′)H_2), 3.26–3.39 (2H, br m, C(2)H_2), 3.47–3.58 (1H, br m, C(4)*H*), 3.86 (3H, s, O*Me*), 5.07–5.16 (1H, C(9b)*H*), 6.90 (1H, d, *J* 8.6, C(6)*H*), 7.77 (1H, dd, *J* 8.6, 1.5, C(7)*H*), 8.01 (1H, d, *J* 1.5, C(9)*H*); δ_C (100 MHz, MeOH-d_4) 22.3 (*C*(3)), 23.4 (*C*(2′)), 29.4 (*C*(1′)), 39.2 (*C*(3′)), 40.9 (*C*(3a)), 44.1 (*C*(2)), 50.9, 50.9 (*C*(4), O*Me*), 57.4 (*C*(9b)), 115.1 (*Ar*), 115.2 (*C*(6)), 119.6 (*Ar*), 130.8 (*C*(7)), 131.4 (*C*(9)), 150.4 (*Ar*), 166.9 (*C*O$_2$Me); *m*/*z* (ESI$^+$) 290 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{24}N_3O_2^+$ ([M+H]$^+$) requires 290.1863; found 290.1862.

4.57. (*S*,*S*,*S*)-*N*(1)-[*N*″-Prenylcarbamimidoyl]-4-[3′-(*N*″-prenylguanidino)propyl]-8-carboxy-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline·*x*TFA [(−)-martinellic acid] 1·*x*TFA

Method A—step 1: A solution of 0.2 M aq NaOH (2 mL) was added to a solution of **80**[15] (39 mg, 55 μmol, >99:1 dr) in MeOH (6 mL) and the resultant mixture was heated at reflux for 16 h. The reaction mixture was then partially concentrated in vacuo to approximately 25% of its original volume and the residue was poured onto satd aq NH_4Cl (25 mL). The aqueous layer was extracted with CH_2Cl_2 (3×10 mL) and the combined organic extracts were washed with brine (10 mL), then dried and concentrated in vacuo.

Method A—step 2: Anisole (60 μL, 0.55 mmol) and TFA (0.12 mL, 1.62 mmol) were added sequentially to a solution of the residue in CH_2Cl_2 (3.5 mL) and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then concentrated in vacuo and the

residue was purified by preparative HPLC[53–55] to give **1**·*x*TFA as a pale yellow oil (13.3 mg, 34% from **80**, >99:1 dr); $[\alpha]_D^{20}$ −118 (*c* 0.3, MeOH); {lit.[1] for sample isolated from natural source $[\alpha]_D$ −8.5 (*c* 0.01, MeOH); lit.[35] $[\alpha]_D^{20}$ −122.7 (*c* 0.31, MeOH); lit.[37] $[\alpha]_D^{29}$ −164.3 (*c* 0.14, MeOH); lit.[7c] $[\alpha]_D^{23}$ −164.8 (*c* 0.33, MeOH)}; ν_{max}(ATR) 3338, 3207 (N−H, O−H) 2980, 2932 (C−H), 1673 (C=O), 1611, 1526, 1452; δ_H (500 MHz, DMSO-d_6) 1.35–1.52 (2H, m, C(1′)H_2), 1.51–1.76 (3H, m, C(3)H_A, C(2′)H_2), 1.63 (3H, s, NCH$_2$CH=C*Me*Me), 1.68 (3H, s, NCH$_2$CH=C*Me*Me), 1.69 (3H, s, NCH$_2$CH=C*Me*Me), 1.73 (3H, s, NCH$_2$CH=C*Me*Me), 2.03–2.14 (1H, m, C(3)H_B), 2.37–2.48 (1H, m, C(3a)*H*), 3.04–3.20 (2H, m, C(3′)H_2), 3.27 (1H, br s, C(4)*H*), 3.33–3.43 (2H, m, C(2)H_2), 3.66–3.77 (2H, m, NCH_2CH=CMe$_2$), 3.79–3.87 (1H, m, NCH_AH$_B$CH=CMe$_2$), 3.88–3.89 (1H, m, NCH$_A$$H_B$CH=CMe$_2$), 5.13–5.20 (1H, m, NCH$_2$C*H*=CMe$_2$), 5.25 (1H, d, *J* 6.4, C(9b)*H*), 5.27–5.34 (1H, m, NCH$_2$C*H*=CMe$_2$), 6.58 (1H, d, *J* 8.5, C(6)*H*), 7.07 (1H, br s, N*H*), 7.43 (2H, br s, 2×N*H*), 7.51–7.62 (2H, br m, 2×N*H*), 7.54 (1H, dd, *J* 8.5, 1.5, C(7)*H*), 7.66 (1H, br s, C(9)*H*), 7.70 (1H, br s, N*H*), 7.78 (1H, br s, N*H*); δ_C (125 MHz, DMSO-d_6) 17.8, 17.9, 25.2, 25.2 (2×NCH$_2$CH=C*Me*$_2$), 25.3 (*C*(2′)), 26.3 (*C*(3)), 33.4 (*C*(1′)), 39.5, 39.8 (2×NCH$_2$CH=CMe$_2$), 40.7 (*C*(3′)), 45.8 (*C*(2)), 49.2 (*C*(4)), 53.0 (*C*(9b)), 113.3 (*C*(6)), 115.7 (*C*(9a)), 116.6 (br q, *J* 299, *C*F$_3$), 117.1 (*C*(8)), 119.2, 119.6 (2×NCH$_2$CH=CMe$_2$), 130.0 (*C*(7)), 130.5 (*C*(9)), 135.6, 136.0 (2×NCH$_2$CH=C*Me*$_2$), 146.3 (*C*(5a)), 154.3, 155.5 (2×NCN), 158.2 (q, *J* 33.4, CF$_3$*C*O$_2^-$), 167.2 (*C*O$_2$H);[56] δ_F (470 MHz, DMSO-d_6) −73.7 (*C*F$_3$); *m*/*z* (ESI$^+$) 496 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{42}N_7O_2^+$ ([M+H]$^+$) requires 496.3395; found 496.3377.

Method B—step 1: NaHCO$_3$ (289 mg, 3.45 mmol) was added to a stirred solution of BrCN (32 mg, 0.30 mmol) and **3**·*x*HCl (40 mg, 0.14 mmol, >99:1 dr) in MeOH (1.5 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 1 h. H$_2$O (1 mL) was added and the resultant mixture was stirred at rt for 15 min. The reaction mixture was then diluted with CH$_2$Cl$_2$ (10 mL) and washed with H$_2$O (2×5 mL). The combined aqueous layers were extracted with CH$_2$Cl$_2$ (5 mL) and the combined organic extracts were dried and concentrated in vacuo to give **85** as a yellow oil (15 mg, >99:1 dr); δ_H (400 MHz, CDCl$_3$) [selected peaks] 3.85 (3H, s, O*Me*) 4.25 (1H, t, *J* 5.1, C(4)*H*), 4.45 (1H, d, *J* 5.1, C(9b)*H*), 4.76 (1H, br s, N*H*), 6.60 (1H, d, *J* 8.6, C(6)*H*), 7.78 (1H, dd, *J* 8.6, 2.0, C(7)*H*), 8.00 (1H, d, *J* 2.0, C(9)*H*).[8a]

Method B—step 2: A solution of prenylamine (35 mg, 0.41 mmol) and **85** (15 mg, >99:1 dr) in HFIP (1.5 mL) was heated in a sealed vial at 110 °C for 5 days, then concentrated in vacuo. The residue was dissolved in MeOH (4 mL) and 0.15 M aq NaOH (1.0 mL) was added. The resultant mixture was heated at reflux for 16 h, then allowed to cool to rt. The reaction mixture was neutralised by addition of 1% TFA in MeOH, and the resultant mixture was concentrated in vacuo. Purification via preparative HPLC[45] gave (−)-martinellic acid **1**·*x*TFA as a yellow oil (6 mg, 6% from **3**·*x*HCl, >99:1 dr).

4.58. (3a*S*,4*R*,9b*S*)-*N*(1)-[*N*′-(*tert*-Butoxycarbonyl)-*N*″-prenylcarbamimidoyl]-4-{3′-[*N*′-(*tert*-butoxycarbonyl)-*N*″-prenylguanidino]propyl}-8-(methoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 81

Et$_3$N (0.45 mL, 3.22 mmol) was added to a solution of **79**·*x*HCl (88 mg, 0.27 mmol, >99:1 dr) and **84** (346 mg, 1.34 mmol) in MeCN/MeOH (2:1, 9 mL) at 40 °C. A solution of AgNO$_3$ (252 mg, 1.48 mmol) in MeCN (2 mL) was added over a period of 30 min. The resultant mixture was stirred at 40 °C (in the dark) for 16 h. The reaction mixture was then filtered through a short pad of Celite® (eluent CHCl$_3$/Et$_3$N, 100:1) and concentrated in vacuo. The residue was dissolved in CHCl$_3$ (30 mL) and the resultant solution was washed with H$_2$O (30 mL). The aqueous layer was extracted with CHCl$_3$ (10 mL) and the combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent CHCl$_3$/MeOH, 97:3) gave **81** as a pale yellow oil, which crystallised slowly on standing to a yellow solid (86 mg, 45%, >99:1 dr); mp 130–136 °C; $[\alpha]_D^{20}$ −52.0 (*c* 0.3, CHCl$_3$); ν_{max} (ATR) 3271 (N−H), 2974, 2931 (C−H), 1715 [C=O (ester)], 1639, 1609 [C=O (carbamate), C=N]; δ_H (400 MHz, CDCl$_3$) 1.44–1.57 (2H, C(2′)H_2), 1.48 (9H, s, C*Me*$_3$), 1.51 (9H, s, C*Me*$_3$), 1.57–1.66 (2H, m, C(1′)H_2), 1.66 (3H, s, NCH$_2$CH=C*Me*$_A$Me$_B$), 1.69 (3H, s, NCH$_2$CH=C*Me*$_A$Me$_B$), 1.72 (3H, s, NCH$_2$CH=CMe$_A$*Me*$_B$), 1.74 (3H, s, CH$_2$CH=CMe$_A$*Me*$_B$), 1.85 (3H, app t, *J* 9.7, C(3)H_2), 2.28–2.40 (1H, m, C(3a)*H*), 3.21–3.51 (5H, m, C(2)H_2, C(4)*H*, C(3′)H_2), 3.71–3.91 (7H, m, O*Me*, 2×NCH_2CH=CMe$_2$), 4.58 (1H br s, N(5)*H*), 5.19–5.27 (1H, m, NCH$_2$C*H*=CMe$_2$), 5.27–5.35 (1H, m, NCH$_2$C*H*=CMe$_2$), 5.85 (1H, d, *J* 6.9, C(9b)*H*), 6.52 (1H, d, *J* 8.4, C(6)*H*), 7.65 (1H, dd, *J* 8.4, 1.8, C(7)*H*), 7.29–7.76 (3H, br m, 3×N*H*), 7.87 (1H, br s, C(9)*H*); δ_C (100 MHz, CDCl$_3$) 18.0, 18.0, 25.6, 25.7 (2×NCH$_2$CH=C*Me*$_2$), 22.6 (*C*(3)), 28.5, 28.5 (2×C*Me*$_3$), 31.0 (*C*(2′)), 39.0 (*C*(3a)), 39.5 (NCH$_2$CH=CMe$_2$), 40.8 (*C*(2)), 42.7 (NCH$_2$CH=CMe$_2$), 47.3 (*C*(3′)), 50.4 (*C*(4)), 51.5 (O*Me*), 56.0 (*C*(9b)), 77.9, 78.1 (2×*C*Me$_3$), 113.6 (*C*(6)), 119.2, 119.6 (*Ar*), 119.8, 120.2 (2×NCH$_2$CH=CMe$_2$), 129.8 (*C*(7)), 131.5 (*C*(9)), 136.9, 137.1 (2×NCH$_2$CH=*C*Me$_2$), 147.7 (*Ar*), 160.1, 162.0, 162.8, 164.0 (2×*C*O, 2×*C*N), 167.3 (*C*O$_2$Me);[57] *m*/*z* (ESI$^+$) 710 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{38}H_{60}N_7O_6^+$ ([M+H]$^+$) requires 710.4600; found 710.4594.

4.59. 2-[3′-(*N*″-Prenylguanidino)propyl]-3-[2″-(*N*″-prenylguanidino)ethyl]-6-carboxy-quinoline·*x*TFA 82·*x*TFA and (3a*S*,4*R*,9b*S*)-*N*(1)-[*N*″-prenylcarbamimidoyl]-4-{3′-[*N*″-prenylguanidino]propyl}-8-carboxy-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline·*x*TFA [(−)-4-*epi*-martinellic acid] 83·*x*TFA

Method A—step 1: A solution of 0.2 M aq NaOH (2 mL) was added to a solution of **81** (35 mg, 49 μmol, >99:1 dr) in MeOH (6 mL) and the resultant mixture was heated at reflux for 16 h. The reaction mixture was then allowed to cool to rt and partially concentrated in vacuo to approximately 25% of its original volume. The residue was poured onto satd aq NH$_4$Cl (25 mL), the aqueous layer was extracted with CH$_2$Cl$_2$ (3×10 mL) and the combined organic extracts were washed with brine (10 mL), then dried and concentrated in vacuo.

Method A—step 2: Anisole (60 μL, 0.55 mmol) and TFA (0.12 mL, 1.62 mmol) were added sequentially to a solution of the residue in CH$_2$Cl$_2$ (3.5 mL) and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then concentrated in vacuo and the residue was purified by preparative HPLC[53,58] to give **83**·*x*TFA as a brown oil (0.8 mg, 2% from **81**, >99:1 dr); $[\alpha]_D^{20}$ −7.1 (*c* 0.31, MeOH); ν_{max} (ATR) 3304, 3177 (O−H, N−H), 2879, 2854 (C−H), 1695 (C=O); δ_H (500 MHz, DMSO-d_6) 1.40–1.78 (5H, m, C(3)H_A, C(1′)H_2, C(2′)H_2), 1.66 (3H, s, NCH$_2$CH=C*Me*Me), 1.70 (3H, s, NCH$_2$CH=C*Me*Me), 1.72 (3H, s, NCH$_2$CH=C*Me*Me), 1.74 (3H, s, NCH$_2$CH=C*Me*Me), 1.97–2.05 (1H, m, C(3)H_B), 2.54 (3H, obsc m, C(2)H_2, C(4)*H*), 3.14–3.24 (2H, m, C(3′)H_2), 3.75 (2H, app t, *J* 5.5, NCH_2CH=CMe$_2$), 3.80–4.05 (2H, m, NCH_2CH=CMe$_2$), 5.20 (1H, t, *J* 6.6, NCH$_2$C*H*=CMe$_2$), 5.31 (1H, d, *J* 6.3, C(9b)*H*), 5.25–5.40 (1H, m, NCH$_2$C*H*=CMe$_2$), 6.57 (1H, br s, N(5)*H*), 6.64 (1H, d, *J* 8.5, C(6)*H*), 7.56 (1H, dd, *J* 8.5, 1.6, C(7)*H*), 7.67 (1H, br s, C(9)*H*), 12.20 (1H, br s, CO_2*H*); δ_C (125 MHz, DMSO-d_6) 17.8, 17.9, 25.3, 25.4 (2×NCH$_2$CH=C*Me*$_2$), 21.3 (*C*(3)), 24.6 (*C*(2′)), 30.1 (*C*(1′)), 40.9 (*C*(3′)), 49.1 (*C*(4)), 113.4 (*C*(6)), 116.9, 117.8 (*Ar*), 119.2, 119.6 (2×NCH$_2$C*H*=CMe$_2$), 128.4 (*Ar*), 129.9 (*C*(7)), 130.5 (*C*(9)), 147.9 (*Ar*), 154.2, 155.5 (2×NCN), 157.8 (q, *J* 32.0, CF$_3$*C*O$_2^-$), 147.9 (*C*O$_2$H);[59] *m*/*z* (ESI$^+$) 496 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{42}N_7O_2^+$ ([M+H]$^+$) requires 496.3395; found 496.3390. Further elution gave **82**·*x*TFA as a pale yellow oil (6 mg, 16% from **81**, >99:1 dr); UV λ_{max} (MeOH) 243 nm (ε 27,453); ν_{max} (ATR) 3327, 3205 (N−H), 2979, 2922 (C−H), 1670, 1636 (C=O, C=N); δ_H (500 MHz, DMSO-d_6) 1.60 (3H, s, NCH$_2$CH=C*Me*Me), 1.65 (3H, s, NCH$_2$CH=C*Me*Me), 1.67 (3H, s, NCH$_2$CH=C*Me*Me), 1.71 (3H, s, NCH$_2$CH=C*Me*Me), 2.04–2.13

(2H, m, C(2′)H_2), 3.05 (4H, app q, J 7.4, C(1′)H_2, C(1″)H_2), 3.31 (2H, app q, J 6.6, C(3′)H_2), 3.57 (2H, app q, J 6.5, C(2″)H_2), 3.69 (2H, app t, J 5.7, NCH_2CH=CMe$_2$), 3.75 (2H, app t, J 5.7, NCH_2CH=CMe$_2$), 5.07–5.13 (1H, m, NCH$_2$CH=CMe$_2$), 5.16–5.23 (1H, m, NCH$_2$CH=CMe$_2$), 7.41–7.72 (8H, m, 8×NH), 8.02 (1H, d, J 8.8, C(8)H), 8.17 (1H, dd, J 8.8, 1.9, C(7)H), 8.30 (1H, s, C(4)H), 8.56 (1H, d, J 1.9, C(5)H); δ_C (125 MHz, DMSO-d_6) 17.7, 17.8, 25.2, 25.3 (2×NCH$_2$CH=CMe_2), 26.6 (C(2′)), 30.6 (C(1″)), 31.3 (C(1′)), 40.5 (C(2″)), 40.6 (C(3′)), 119.1, 119.2 (2×NCH$_2$CH=CMe$_2$), 125.9 (C(8a)), 128.2 (C(8)), 128.4 (C(7)), 130.1 (C(5)), 131.3 (C(3)), 136.0, 136.0 (2×NCH$_2$CH=CMe_2), 137.1 (C(4)), 147.3 (C(4a)), 155.5, 155.6 (2×NCN), 158.3 (q, J 34.3, $CF_3CO_2^-$), 162.7 (C(2)), 167.0 (C(6)), 173.1 (CO_2H);[60] δ_F (470 MHz, DMSO-d_6) −74.2 ($CF_3CO_2^-$); m/z (ESI$^+$) 494 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{40}N_7O_2^+$ ([M+H]$^+$) requires 494.3238; found 494.3230.

Method B—step 1: $NaHCO_3$ (71 mg, 0.84 mmol) was added to a stirred solution of BrCN (8 mg, 74 μmol) and **79**·xHCl (20 mg, 34 μmol, 99:1 dr) in MeOH (1.5 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 1 h H_2O (1 mL) was added and the reaction mixture was stirred at rt for 15 min, then diluted with CH_2Cl_2 (10 mL) and washed with H_2O (2×5 mL). The combined aqueous layers were extracted with CH_2Cl_2 (5 mL) and the combined organic extracts were dried and concentrated in vacuo to give **87** as a yellow oil (9 mg, >99:1 dr); δ_H (400 MHz, $CDCl_3$) [selected peaks] 3.87 (3H, s, OMe), 4.82 (1H, d, J 7.8, C(9b)H), 6.55 (1H, d, J 8.6, C(6)H), 7.76 (1H, dd, J 8.6, 1.9, C(7)H), 8.13 (1H, d, J 1.9, C(9)H).

Method B—step 2: A solution of prenylamine (5.7 mg, 67 μmol) and **87** (9 mg, >99:1 dr) in HFIP (1.5 mL) was stirred in a sealed vial at 110 °C for 5 days, then concentrated in vacuo. The residue was dissolved in MeOH (4 mL) and 0.15 M aq NaOH (1.0 mL) was added. The resultant mixture was heated at reflux for 16 h, then allowed to cool to rt. The reaction mixture was neutralised by addition of 1% TFA in MeOH, and the resultant mixture was concentrated in vacuo. Purification via preparative HPLC[58] gave 4-*epi*-martinellic acid **83**·xTFA as a yellow oil (0.7 mg, 3% from **79**·xHCl, >99:1 dr); $[\alpha]_D^{20}$ −12.6 (c 0.31, MeOH).

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.09.013.

References and notes

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19. Crystallographic data (excluding structure factors) for the structures of **19**, **20**, **24**, **26**, **33**, **36** and **50** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 951639–951645, respectively.
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23. (*R*)-*N*-Allyl-*N*-(α-methylbenzyl)amine was prepared in 91% yield by treatment of (*R*)-α-methylbenzylamine (>99:1 er) with BuLi at 0 °C in THF, followed by addition of allyl bromide. Subsequent deprotonation with BuLi in THF generated a solution of the lithium amide reagent.
24. In both **33** and **50**, the *N*(5)-Boc group adopts a conformation in which it is perpendicular to the ring system; in this conformation it is not able to become conjugated with the *N*(5)-lone pair.
25. Ding, R.; He, Y.; Xu, J.; Chen, Y.; Feng, M.; Qi, C. *Molecules* **2011**, *16*, 5665.
26. The complicated nature of the ^{1}H NMR spectrum of the crude reaction mixture prevented the determination of an accurate product distribution.
27. For example, see: Seo, J.; Martásek, P.; Roman, L. J.; Silverman, R. B. *Bioorg. Med. Chem. Lett.* **2007**, *15*, 1928.
28. Tetracyclic products arising from intramolecular displacement of a C(3′) substituent by the aniline have previously been observed in related systems; see: Refs. 7a,5l
29. Bull, S. D.; Davies, S. G.; Fenton, G.; Mulvaney, A. W.; Shyam Prasad, R.; Smith, A. D. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3765.
30. Hungerhoff, B.; Samanta, S. S.; Roels, J.; Metz, P. *Synlett* **2000**, 77.
31. (*R*)-*N*-Allyl-*N*-(α-methyl-*p*-methoxybenzyl)amine was prepared in 90% yield by treatment of (*R*)-α-methylbenzylamine (>99:1 er) with BuLi at 0 °C in THF, followed by addition of allyl bromide. Subsequent deprotonation with BuLi in THF generated a solution of the lithium amide reagent.
32. Repetition of the reaction for both **52** and **53** with excess NaH (3.0 equiv) resulted in substantial decomposition to mixtures of unidentified products.
33. Couturier, M.; Andresen, B. M.; Tucker, J. L.; Dubé, P.; Negri, J. T. *Org. Lett.* **2001**, *3*, 465.
34. For the use of this reaction as a hydrogen source, see: Couturier, M.; Andresen, B. M.; Tucker, J. L.; Dubé, P.; Brenek, S. J.; Negri, J. T. *Tetrahedron Lett.* **2001**, *42*, 2763.
35. The corresponding chloride was not observed in this case.
36. Davies, S. G.; Whitham, G. H. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2279.
37. Caddick, S.; Judd, D. B.; Lewis, A. K.; Reich, M. T.; Williams, M. R. V. *Tetrahedron* **2003**, *59*, 5417.
38. The synthesis of a racemic sample of **62** has been reported previously, see: Ref. 5b.
39. 2-Iodo-4-bromoaniline **63** is commercially available, although it can be produced in quantitative yield at far less cost from 2-iodoaniline by treatment with KBr, $NaBO_3 \cdot 4H_2O$ and ammonium molybdate in AcOH; see Roche, D.; Prasad, K.; Repic, O.; Blacklock, T. J. *Tetrahedron Lett.* **2000**, *41*, 2083.
40. The relative and absolute configurations within both **66** and **67** were unambiguously established by single crystal X-ray diffraction analyses. Crystallographic data (excluding structure factors) for the structures of **66** and the *N*(5)-deprotected derivative of **67** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 926034 and 926035, respectively; see Ref. 15.
41. Phosphorane **38** could not be used in this case as it was not possible to separate the product **67** from the excess phosphorane **38** and the Ph_3PO residues.
42. For examples of the use of 2-pyridyl phosphoranes, see: (a) Cafici, L.; Pirali, T.; Condorelli, F.; Del Grosso, E.; Massarotti, A.; Sorba, G.; Canonico, P. L.; Tron, G. C.; Genazzani, A. A. *J. Comb. Chem.* **2008**, *10*, 732; (b) O'Brien, M.; Denton, R.; Ley, S. V. *Synthesis* **2011**, 1157.
43. Similar fragmentation pathways have been observed in related hexahydropyrroloquinoline systems; see: Ref. 6b.
44. The procedure reported by Snider, et al. reports heating **85** and prenylamine in HFIP at 120 °C in a sealed tube.
45. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.
46. Compounds **34** and **51** were isolated as single diastereoisomers (>99:1 dr) of unknown configuration at C(4).
47. Peaks corresponding to *C*(3) and *C*(3a) were not observed in the ^{13}C NMR spectrum of **61**; however, resonances corresponding to *C*(3) and *C*(3a) were observed at 27.8 and 42.3 ppm, respectively, in the HSQC spectrum of **61**.
48. For ^{1}H and ^{13}C NMR data for (±)-**62**, see: Ref. 5b.
49. The presence of **74** could be distinguished by TLC analysis and by the observation of characteristic B–H stretches in the IR spectrum of the crude reaction mixture: ν_{max} (ATR) 2368, 2273 (B–H).
50. A peak corresponding to NCO was not observed in the ^{13}C NMR spectrum of **74**.
51. Peaks corresponding to *C*(3) and *C*(3a) were not observed in the ^{13}C NMR spectrum of **75**; however, a resonance corresponding to *C*(3a) was observed at 43.4 ppm in the HSQC spectrum of **75**.
52. A peak corresponding to *C*(3a) was not observed in the ^{13}C NMR spectrum of **78**; however, a resonance corresponding to *C*(3a) was observed at 43.8 ppm in the HSQC spectrum of **78**.
53. The authors would like to thank Veronique Gouverneur and Stefan Verhoog for their assistance with the purification of **1**·*x*TFA, **82**·*x*TFA and **83**·*x*TFA
54. Purification of **1**·*x*TFA was conducted using a SunFire™ preparative column (C_{18}, 10 μm, 10×250 mm) eluting with H_2O/MeOH/CF_3CO_2H (80:20:0.1 → 20:80:0.1, gradient elution) for 40 min with a flow rate of 2.50 mL/min. The detector was set to 330 nm and the major component had a retention time of 19.1 min.
55. Although several literature reports begin the solvent gradient in 80:20 H_2O/MeOH, this is not a suitable solvent system to load the crude material. After optimisation, it was found best to dissolve the crude sample in ~500 μL of MeOH and perform purification with several ~125 μL injections.
56. The remaining peak in the ^{13}C NMR spectrum, corresponding to *C*(3a) within **1**·*x*TFA, was obscured by the resonances corresponding to PhMe-d_8.
57. A peak corresponding to *C*(1′) was not observed in the ^{13}C NMR spectrum of **81**; however, a resonance corresponding to *C*(1′) was observed at 25.8 ppm in the HSQC spectrum of **81**.
58. Purification of **82**·*x*TFA and **83**·*x*TFA was conducted using a SunFire™ preparative column (C_{18}, 10 μm, 10×250 mm) eluting with H_2O/MeOH/CF_3CO_2H (80:20:0.1 → 20:80:0.1, gradient elution) for 40 min with a flow rate of 2.50 mL/min. The detector was set to 330 nm, and **82**·*x*TFA and **83**·*x*TFA had retention times of 21.9 and 20.4 min, respectively.
59. Peaks corresponding to *C*(2), *C*(3a) *C*(9b), CF_3 and both $NCH_2CH{=}CMe_2$ groups were not observed in the ^{13}C NMR spectrum of **83**·*x*TFA; however, a resonance corresponding to *C*(9b) was observed at 56.1 ppm in the HSQC spectrum of **83**·*x*TFA.
60. Peaks corresponding to CF_3 and both $NCH_2CH{=}CMe_2$ groups were not observed in the ^{13}C NMR spectrum of **82**·*x*TFA.